XI-E. Blood Cells and Plasma

The most consistent effect of the carbon monoxide component of cigarette smoking is the appearance of carboxyhemoglobin in the blood. The molecular basis for the formation of carboxyhemoglobin has been reviewed by Rossi-Fanelli and Antonini (1958), Wittenberg (1966) Keyes et al. (1967), Oski et al. (1970), Bunn and Jandl (1970) and Brewer et al (1970, 1971) There is a change in oxygen-dissociation curve of blood of smokers (Gutenkauf et al., 1967) and patients with acute myocardial infarction (Eliot and Mizukami, 1967). There is an increase in oxygen affinity of the hemoglobin presumably unrelated to carboxyhemoglobin. The consequences of the presence of carboxyhemoglobin to the circulatory system have been reviewed by Lilienthal (1950), Bartlett (1968), Goldsmith and Landow (1968), Grut et al. (1970) and DuBois (1970).

Exposure to carbon monoxide causes an increase in platelet adhesiveness in atherosclerotic patients (El-Ebrashy et al., 1967) and in rabbits (Birnstingl et al., 1971). There is also an increase in fibrinolytic activity in patients suffering from carbon monoxide poisoning (El-Attar, 1968 a and b) and in experimental animals (Candura and Craveri, 1964).

Four groups of situations are characterized by hematologic changes. They are as follows:

1. Exposure to carbon monoxide in man causes an increase in the red cell and reticulocyte counts and the serum globulin fraction (Coscia et al.,

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1964; Tkachenko et al., 1966; Glass et al., 1968; Kjeldsen and Damgaard, 1968; Bethlenfalvay, 1971a). The erythrocytes manifest some differences from normal erythrocytes in staining (Blackmore, 1970; Bethlenfalvay, 1971b), denaturation of hemoglobin (Perrelli et al., 1970) and a change in the shift of the oxyhemoglobin dissociation curve to the left (Brody and Coburn, 1969).

2. In dogs, exposure to carbon monoxide increases hemoglobin concentration (Asmussen and Vinther-Paulsen, 1949). This change is regarded as an important mechanism for tolerance of acclimatization to carbon monoxide (Otis, 1970). A similar increase in hemoglobin and the red cell count has been noted in other species, such as rabbits (Truhaut et al., 1968), rats (Ramsey, 1969), rhesus monkeys (Theodore et al., 1971), and squirrel monkeys (Jones et al., 1971).

3. Cigarette smoking caused an increase in the red cell count and hemoglobin, whereas abstinence caused a fall in the content of these in humans (Eisen and Hammond, 1956; Pincherle and Shanks, 1967) and in hamsters (Reckzeh and Dontenwill, 1970). In another investigation involving smokers, the elevated hemoglobin and red cell count were correlated with carboxyhemoglobin levels (Petrovic, 1970). A shift in the oxygen dissociation curve to the left has been noted in cigarette smokers (Gutenkauf et al., 1967; Birnstingle et al., 1967).

4. Patients suffering from myocardial ischemia with normal coronary arteriograms have been shown to have abnormal hemoglobin-oxygen dissociation

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(Likoff et al., 1967; Eliot and Bratt, 1969; Guy et al., 1971). There is no evidence that these patients sustain carboxyhemoglobinemia, nor is the ischemia associated with cigarette smoking.

The above examples are clearly different entities. Cigarette smoking is included only in situation 3 and carbon monoxide 1 to 3.

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PART SIX

PUBLICATIONS AND RECOMMENDATIONS

XII. Secondary Publications on Smoking and Heart Disease

XIII. Publications in Defense of Smoking

XIV. Commentary on US Public Health Publications

XV. Recommendations to the Council for Tobacco Research

The last group of sections is largely a commentary on the US Public Health Publications on "Smoking and Health." Following the appearance of the first Surgeon General's Report in 1964, several secondary publications have appeared accepting the statement that smoking is causally related to coronary heart disease. There are only a few publications which challenge this statement. A list of recommendations to the Council for Tobacco Research concludes this report.

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

The publications listed in this section are secondary to those which describe the original investigations covered in preceding sections. Since 1864, there has been an increase in the number of publications accepting the Surgeon General's statement that smoking is causally related to coronary heart disease. The number of review articles, editorials, letters and special articles has increased so rapidly that the total number appearing since 1970 approaches the number of articles appearing up to 1964. The total number at various periods is as follows:

	1879-1949	1950-1964	1965-1969	1970-1973
A. Review articles (p. 323)	22	22	14	6
B. Special articles (p. 328)	1	14	29	17
C. Letters to the Editor (p. 332)	1	17	14	26
D. Editorials (signed) (p. 336)	—	14	14	6
E. Editorials (unsigned) (p. 339)	—	14	18	15
F. Miscellaneous articles (p. 342)	—	—	23	7
Total number of articles	24	81	112	77

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

A. Review Articles

Reprint

1879

DECAISNE D E: Les femmes qui fument. Rev d'Hygiene Police Sanitaire 1: 914-922, 1879. S 1

1883

VALLIN E: Sur quelques accidents causés par le tabac. Rev Hyg 5: 223-237, 1883. S 2

1885

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1887

FAVARGER H: Chronische Tabakvergiftung und ihren Einfluss auf das Herz und den Magen. Wien Med Wochenschr 37: 324-326, 1887. S 4

1892

CHAPMAN W C: Tobacco as a cause of hypertrophy and dilatation of the heart: "The tobacco-heart" with a report of cases. Med News 61: 733-735, 1892. S 5

1902

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1905

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1906

BRUNTON L: The effect of tobacco in health and disease. Med Exam Pract 16: 148-150, 1906. S 8

KAKOWSKI: Ueber den direkten Einfluss verschiedner Substanzen auf das Herz. Arch Int Pharmacodyn Ther 15: 21-139, 1906. S 9

1917

SIEBELT: Tabakmissbrauch in ursächlichem Zusammenhange mit Kriegsneurosen, vor allem des Herzens. Med Klin 13: 68-69, 1917. S 10

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Reprint

1921

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1923

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1926

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1929

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1930

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1937

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1939

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1943

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1944

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1946

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1949

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XII A: Review Articles

Reprint

1950

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1952

SCOTT R B: Some medical aspects of tobacco-smoking. Br Med J 1: 671-675, 1952. S 23

1954

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1956

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1958

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1962

DELARUE N C: Cigarette smoking: A clinical and public health challenge. Can Med Assoc J 87: 961-969, 1962. S 37

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1963

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1964

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GIOVANELLI E: Gli effetti del fumo di tabacco sul cuore e sue possibili influenze nell'insorgenza e nel decorso delle affezioni cardiache. Minerva Med 55: 1529-1542, 1964. S 41

PAUN D: Tabak und Koronarinsuffizenz. Z Aerztl Fortbild 58: 690-693, 1964. S 42

SCHIRGER A and SHICK R M: Tobacco in cardiovascular disease. Minn Med 47: 129-132, 1964. S 43

1965

CRAMER K: Rökning och coronarsjukdom. Lakartidningen 62: 2532-2540, 1965. S 44

RAAB W: Origin, prediction and prevention of ischemic heart disease. J Circ J 29: 113-122, 1965. S 45

1967

ANSELMINO A and BOSCO M: Tabacco e cuore. Minerva Med 58: 1298-1308, 1967. S 46

KREYBERG L, DABLE T, POPPE E, EFSKIND L, PEDERSEN E, ELDJARN L, and DEVIK F: Tobakkroking og helse. Tidsskr Nor Laegeforen 87: 1007-1013, 1967. S 47

1968

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Reprint

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1970

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GODBER G E: Smoking disease: A self-inflicted injury. Am J Public Health 60: 235-242, 1970. S 59

1971

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1972

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1951

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1958

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1960

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1962

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1963

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1964

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BLAKE J M: Self-induced air pollution: smoking. N Y State J Med 64: 806-810, 1964. S 71

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FLICK J B Jr: The cigarette smoking problem. Delaware Med J 36: 51-53, 1964. S 73

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Reprint

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OCAMPO OTERO A: Efectos perjudiciales del tabaco. Med Segruided Trabajo Madrid 12: 78-82, 1964. S 76

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KISTLER H J: Coronare Herzkrankheit und Zigarettenrauchen. Schweiz Med Wochenschr 95: 436-437, 1965. S 80

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1966

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Reprint

1968

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FISHER G R: Associated clinical societies. Delaware Med J 40: 364-365, 1968. S 93

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PAUL O: Stimulants and coronaries. Postgrad Med 44: 196-199, 1968. S 101

SCHUMANN L M: Epidemiology of smoking related diseases which physicians encounter in their office practice. Dis Chest 54: 8-11, 1968. S 102

TERRIS M: A social policy for health. Am J Public Health 58: 5-12, 1968. S 103

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DLIN B M: The doctor, his emotions and his heart. Minn Med 52: 369-374, 1969. S 104

DOYLE J T: Cigarette smoking. The associated cardiovascular risk. Minn Med 52: 1311-1313, 1969. S 105

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SACKETT D L: Cigarettes, alcohol, hospitals, and atherogenesis. Am Heart J 78: 423-424, 1969. S 107

1970

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MUSHIN W W: The normality of the abnormal. Anesth Analg 49: 667-679, 1970. S 111

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1971

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BALL K H: Cigarettes and the prevention of heart disease. Rehabilitation 25: 17-20, 1972. S 122

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		Reprint
1934		
	BLUMER G: The relation of the use of alcohol and tobacco to coronary occlusion. JAMA 102: 1177, 1934.	S 125
1951		
	PARNELL R W: Smoking and cancer. Lancet 1: 963, 1951.	S 126
1953		
	LEVY R L, KNIGHT G F, MYERSON M C and ROSEN F L: Effects of tobacco smoking. Mod Med 21: 120-121, 1953.	S 127
1955		
	OLBERT T: Smoking and the heart. Lancet 2: 1041, 1955.	S 128
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	ACHESON R M: Atherosclerosis and coronary heart disease. Lancet 2: 706, 1960.	S 130
	CHARTERS A D and ARYA B P: Incidence of ischaemic heart disease among Indians in Kenya. Lancet 1: 288-289, 1960.	S 131
	RIGDON R H: The smoking controversy. JAMA 173: 293-295, 1960.	S 132
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	HUGHES J P W: Civilisation and peptic ulcer. Lancet 1: 322, 1962.	S 135
	LUKE E: Addiction to mentholated cigarettes. Lancet 1: 110-111, 1962.	S 136
	RIGDON R H: To the editor. Ind Med Surg 31: 235, 1962.	S 137
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BURCH P R J and ROWELL N R: Smoking and atherosclerosis. Br Med J 1: 1050-1051, 1966. S 147

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1967

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1968

ASHER R: Trial of unsaturated-fat diet. Lancet 2: 1191, 1968. S 151

GRANT B J B: The nicotine habit. Lancet 1: 645, 1968. S 152

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PAFFENBARGER R S: Occupational preselections. N Engl J Med 283: 100, 1970. S 159

YUDKIN J: Sugar, cigarettes, and heart-disease. Lancet 1: 1111, 1970. S 160

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NAHUM L H: Smoking and physiological age. Conn Med 26: 593-594, 1962. S 186

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HAMMOND E C: Intelligent debate or demented fiddling? Can Med Assoc J 96: 679-680, 1967. S 198

PAGE I H and ALVAREZ W C: Cigarettes and the ambivalent American. Mod Med 35: 59-61, 1967. S 199

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REID D D: Smoking and the heart. Health 5: 176-177, 1968. S 203

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XII D: Editorials (Signed) — Reprint

LITTLE D M Jr: Physician, heal thyself. Anesthesiology 35: 1-3, 1971. — S 215

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1955

British Medical Journal: Smoking and coronary thrombosis. 1: 91-92, 1955. S 21

1956

British Medical Journal: Smoking and the cardiovascular system. 2: 90, 1956. S 21

1963

British Medical Journal: Prevention of myocardial infarction. 2: 1351-1352, 1963. S 22

British Medical Journal: Smoking and blood clotting. 1: 833-834, 1963. S 22

Journal of the American Medical Association: Tobacco, pollution, and pesticides. 155: 31-33, 1963. S 22

1964

American Journal of Public Health: Cigarette smoking and health. 54: 322-324, 1964. S 22

British Medical Journal: Work after a "coronary". 2: 703-704, 1964. S 22

British Medical Journal: Healthier life. 1: 1267-1268, 1964. S 22

British Medical Journal: Smoking and death. 1: 192-194, 1964. S 22

Canadian Medical Association Journal: Smoking once more. 91: 353-354, 1964. S 22

Journal of the American Medical Association: Childish habit. 189: 850, 1964. S 22

Lancet: Haemoglobin changes in Buerger's disease. 2: 1164, 1964. S 22

Lancet: Coronary-artery disease in the young. 2: 628-629, 1964. S 23

Medical Journal of Australia: The United States report on smoking and health. 51: 201-202, 1964. S 23

1965

Medical Journal of Australia: National health. 1: 205-206, 1965. S 23

Public Health Reports: Relate heavy cigarette smoking to angina. 60: 121, 1965. S 23

1966

British Medical Journal: Smoking and atherosclerosis. 1: 755-756, 1966. S 23

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XII E: Editorials (Unsigned) Reprint

Journal of the American Medical Association: The martyred meal. 198: 1362-1363, 1966. S 236

1967

Boletin de la Association Medica de Puerto Rico: Cigarette smoking and health characteristics. 59: 293-295, 1967. S 237

1968

Food and Cosmetics Toxicology: The scourge of the tobacco industry. 6: 797-799, 1968. S 238

Journal of the Medical Association of Georgia: Coronary heart disease and smoking. 58: 440, 1968. S 239

Medical Journal of Australia: Social status and coronary heart disease. 2: 635-636, 1968. S 240

Medical Officer: Royal institute of Public Health and Hygiene conference, Bristol. 120: 187-190, 1968. S 241

Philadelphia Medicine: Cigarette smoking -- A call to arms. 64: 587, 1968. S 242

1969

American Journal of Public Health: Life styles in the prevention of coronary heart disease. 59: 1568-1569, 1969. S 243

British Medical Journal: Menace of smoking. 3: 753-754, 1969. S 244

British Medical Journal: Coronary disease and competitiveness. 1: 1-2, 1969. S 245

Lancet: More effects of cigarettes. 1: 1012-1013, 1969. S 246

Lancet: Blood-groups and serum-cholesterol. 2: 625, 1969. S 247

Medical Journal of Australia: Smoking and health. 1: 84, 1969. S 248

Public Health Report: Smoking and health. 83: 225, 1968. S 249

1970

Circulation: Some problems. 41 (Suppl 1): 184-185, 1970. S 250

Lancet: The longshoreman's life. 2: 87, 1970. S 251

Lancet:

Medical Journal of Australia: Myocardial infarction and cerebrovascular accidents. 2: 1106, 1970. S 253

Medical Journal of Australia: To smoke or not to smoke. 1: 346-347, 1970. S 254

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XII E: Editorials (Unsigned)

Reprint

1971

British Medical Journal: Coronary deaths. 4: 64, 1971. S 255

British Medical Journal: World action on smoking. 4: 64, 1971. S 256

British Medical Journal: The smoking disease. 1: 61-62, 1971. S 257

Journal of the American Medical Association: Exercise and the heart. 215: 974-975, 1971. S 258

Journal of the American Medical Association: Prevention of CHD: The fat's in the fire. 215: 1813, 1971. S 259

Lancet: Counterblasts to tobacco. 1: 69-70, 1971. S 260

New Zealand Medical Journal: The coronary problem. 74: 332-335, 1971. S 261

1972

British Medical Journal: Predicting coronary artery disease. 4: 3, 1972. S 262

British Medical Journal: Smoking and vascular disease. 2: 3-4, 1972. S 263

Canadian Medical Association Journal: Smoking and health. 106: 313, 1972. S 264

1973

American Journal of Clinical Nutrition: Diet and coronary heart disease. 26: 53-54, 1973. S 265

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F. Miscellaneous Articles

Reprint

1963

Journal of the American Medical Association: Cigarette smoking and blood lipids. 184: 201-202, 1963. S 266

Medical Science: Cardiology. Coronary disease in young people. 13: 720, 722, 1963. S 267

1964

Pennsylvania Medical Journal: Predisposing factors in coronary heart disease. 67: 36, 1964. S 268

Pennsylvania Medical Journal: Pulmonary emphysema and the heart. 67: 24, 1964. S 269

1965

Medical College of Virginia Quarterly: Panel on atherosclerosis. 1: 36-39, 1965. S 270

Quarterly Journal of Medicine: 34: 484, 1965. S 271

1966

Journal of the Medical Association of America: Smokers' blood clots more rapidly. 197: 36, 1966. S 272

Journal of the Medical Association of America: Coronary disease prognosis sought from 100,000 persons. 197: 46-47, 1966. S 273

Pennsylvania Medicine: Public health aspects of heart disease. 66: 41, 1966. S 274

1967

El Dia Medico: La costumbre de fumar. 265, 1967. S 275

1968

British Medical Journal: Smoking habits. 1: 64-65, 1968. S 276

Bulletin of the Los Angeles City Medical Association: Smoking and chronic bronchopulmonary disease. 98: 57-58, 1968. S 277

Bulletin of the Los Angeles City Medical Association: The health consequences of smoking. A public health review: 1967. 1-2, 1968. S 278

Disease of the Chest: Formal recommendations of the National Forum on office management of smoking problems. 4-5, 1968. S 279

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XII F: Miscellaneous Articles

	Reprint
Hospital Medicine: Axioms on coronary heart disease. 4: 71, 1968.	S 280
Missouri Medicine: Miscellany. 65: 711-712, 1968.	S 281
1969	
British Heart Journal: Dietry sugar intake and ischaemic heart disease. 31: 792-793, 1969.	S 281
British Medical Journal: Cigarette advertising. 2: 833, 1969.	S 282
El Dia Medico: Las enfermedades de la civilizacion. 856, 1969.	S 283
Journal of the American Medical Association: Call for cigarette curbs. 210: 2293, 1969.	S 284
Journal of the American Medical Association: Researchers say smoking causes aortic atherosclerosis. 207: 664-666, 1969.	S 285
Medicina Sociale: Congressi e riunioni di interesse medico-sociale. 19: 73-74, 1969.	S 286
Pediatria de Actualidad: Aterosclerosis en Pediatria. , 1969.	S 287
1970	
British Medical Journal: Labelling of cigarette packets. 1: 312, 1970.	S 288
Canadian Medical Association Journal: No smoking signs at WHO Headquarters. 102: 996, 1970.	S 289
Journal of the American Medical Association: The good life and long life just may go together. 214: 1636, 1970.	S 290
1971	
Schweizerische Medizinische Wochenschrift: Ärzte als Zigarettenraucher 101: 1420-1421, 1971.	S 291
1972	
Journal of the American Medical Association: Psychiatrists shrink from giving up cigarettes. 219: 823, 826-828, 1972.	S 292
Journal of the American Medical Association: Carbon monoxide linked to heart disease. 221: 456-457, 1972.	S 293
Modern Medicine: Heart research offers a boost for exercise -- and a warning. 40: 26, 28, 1972.	S 294

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XIII. PUBLICATIONS IN DEFENSE OF SMOKING

The 35 articles listed in this section include eight articles which challenge the conclusions that appeared in the Surgeon General's Report. The following articles are quoted in the Commentary Section.

	Copies appearing on page
Examination of statistical methods:	
Brownlee K A: A review of "Smoking and Health". J Am Stat Assoc 60: 722-739, 1965.	353 (a)
Saiger G L: A critique on the report of the Surgeon General's advisory committee on smoking and health. Bull Int Stat Inst 41: 856-860, 1966.	357 (a)
Sterling T D: A review of the claim that excess morbidity and disability can be ascribed to smoking. J Am Stat Assoc 66: 251-257, 1971.	461 (a)
Oster K A: Prevention of atherosclerosis: Fact or fiction? Med Counterpoint 4: 13-27, 1972.	344 (a)
Examination of epidemiologic and experimental data:	
Cohen J and Heimann R K: Heavy smokers with low mortality. Ind Med Surg 31: 115-120, 1962.	352 (a)
Hutchison G B: The nature of epidemiologic evidence: Smoking and health. Bull N Y Acad Med 44: 1471-1475, 1968.	355 (a)
Seltzer C C: An evaluation of the effect of smoking on coronary heart disease. JAMA 203: 193-200, 1968.	382 (a)
Seltzer C C: The effect of cigarette smoking on coronary heart disease. Arch Environ Health 20: 418-423, 1970.	425 (a)

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ANONYMOUS: Bulletin on tobacco. N Engl J Med 268: 1087, 1963.	S 29
ANONYMOUS: The Canadian Medical Association brief to the National Conference on Smoking and Health, Ottawa. 89: 1154-1156, 1963.	S 29
ANONYMOUS: The Association presents its views about smoking. Coll Health 14: 2-3, 1965.	S 29
ANONYMOUS: Studies broaden data on smoking and health. JAMA 210: 1377-1378, 1967.	S 29
ANONYMOUS: Cigarette consumption down slightly after five years of smoking debate. JAMA 207: 475-476, 1969.	S 30
ANONYMOUS: The air we breathe. JAMA 208: 353, 1969.	S 30
ANONYMOUS: The longshoreman's life. Lancet 2: 87, 1970.	S 30
ANONYMOUS: Should a strong attempt be made to get old people to change habits like smoking and overeating. Geriatrics 25: 68, 71, 1970.	S 30
ANONYMOUS: Does it help to stop smoking? Lancet 1: 238-239, 1972.	S 30
ANONYMOUS: Cigarettes and heart disease. N Engl J Med 284: 1384, 1971.	S 30
ALTSCHULE M D: Dangerous living. Med Sci 13: 337, 1963.	S 30
ARNOLD C B: Smoking and coronary atherosclerosis. N Engl J Med 273: 1284-1285, 1965.	S 30
BELL J A E: Mortality rates of smokers. Chem Eng News 48: 1970.	S 30
BERKSON J: Statistics and tobacco. JAMA 172: 967-969, 1960.	S 30
BOURKE G J: The opinions of some medical students on smoking, career, and fluoridation. J Ir Med Assoc 154-156, 19	S 31
BRASS A: Tobacco and health. Report of Scottsdale Research Conference. JAMA 213: 1879-1880, 1970.	S 31
BROWN R C: Manifestations of atherosclerosis. JAMA 222: 488, 1972.	S 31
BROWNLEE K A: A review of "Smoking and Health". J Am Statist Assoc 60: 722-739, 1965.	S 31
CHEDD G and STUBBS P: Smoking may not cause coronaries. New Scientist 43: 222, 1961.	S 31
COHEN J and HEIMANN R K: Heavy smokers with low mortality. Ind Med Surg 31: 115-120, 1962.	S 31

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FIESSINGER C: Tobacco angina pectoris. JAMA 60: 1473, 1913. S 316

HUTCHISON G B: The nature of epidemiologic evidence: Smoking and health. Bull N Y Acad Med 44: 1471-1475, 1968. S 317

JORES A: Arzt, Tabak und Alkohol. Dtsch Arzt 13: 752, 754-755, 1964. S 318

KASPARIAN H: Ethanol, smoking evaluated with coronary blood flow. JAMA 190: 33, 1964. S 319

MAJEKODUNMI M A: Seventeenth World Health Assembly. WHO Chron 18: 117-127, 1964. S 320

OSTER K A: Predisposition to atherosclerosis. JAMA 222: 704, 1972. S 321

OSTER K A: Prevention of atherosclerosis: Fact or fiction? Med Counterpoint 4: 13-27, 1972. S 322

SAIGER G L: A critique on the report of the Surgeon General's advisory committee on smoking and health. Bull Int Stat Inst 41: 856-860, 1966. S 323

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SELTZER C C: An evaluation of the effect of smoking on coronary heart disease. JAMA 203: 193-200, 1968. S 325

SELTZER C C: The effect of cigarette smoking on coronary heart disease. Arch Environ Health 20: 418-423, 1970. S 326

SOMMER R M: Nonspecification of tobacco smokers. JAMA 222: 487, 1972. S 327

STERLING T D: A review of the claim that excess morbidity and disability can be ascribed to smoking. J Am Stat Assoc 66: 251-257, 1971. S 328

WALKER A R P: The prevention of coronary heart disease. Am Heart J 72: 721-724, 1966. S 329

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XIV. COMMENTARY ON US PUBLIC HEALTH PUBLICATIONS

After the text of this review article was completed, the seven volumes relating to "Smoking and Health" issued by the Surgeon General was examined. The pages relating to cardiovascular disease are reproduced on yellow paper and commentaries appear on the succeeding pages. It can be noted that there are differences in interpretation of the state of knowledge at the time the Surgeon General's Reports appeared in 1964, 1967, 1968, 1969, 1971, 1972, and 1973.

		Commentary starts on page
1964	The Health Consequence of Smoking pp. 315-334	348
1967	Smoking and Health pp. 45-86	356
1968	Smoking and Health pp. 15-61	372
1969	Smoking and Health pp. 9-134	394
1971	Smoking and Health pp. 15-134	405
1972	Smoking and Health pp. 11-34	460
1973	Smoking and Health (draft available)	471

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SMOKING *and* HEALTH

REPORT OF THE ADVISORY COMMITTEE
TO THE SURGEON GENERAL
OF THE PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

Chapter 11

Cardiovascular Diseases

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Chapter 11

INTRODUCTION

It has been suggested repeatedly that smoking may have adverse effects on the cardiovascular system. Recently, studies of large groups of people have shown that cigarette smokers in particular are more prone to die early of certain cardiovascular disorders than non-smokers. Chief among these disorders is coronary artery disease, and the present chapter deals mostly with this subject. The chapter begins with a summary of information about the acute effects of smoking on the cardiovascular system. This is followed by a brief account of coronary disease, its frequency in different kinds of people, and the many factors known or thought to affect the likelihood of its development. The aim here is not to review critically our knowledge of coronary disease but only to give background for what follows. Next is summarized the information currently available from study of large population groups on the association of cigarette smoking with an increased tendency to have coronary disease. There follows a brief discussion of smoking and non-coronary cardiovascular disease. Finally, there is a short review of evidence relating to the question of whether cigarette smokers may, as a group, differ from non-smokers in ways not caused by smoking itself. Mortality ratios showing the association between cigarette smoking and deaths from cardiovascular disease, especially coronary disease, do not indicate the magnitude of the burden. This can be better appreciated from consideration of the following facts: cardiovascular disease deaths now total more than 700,000 annually in the United States. Of these more than 660,000 were due to heart disease, with more than 560,000 due to arteriosclerotic heart disease including coronary disease. The remaining approximately 40,000 were ascribed to disease of other parts of the cardiovascular system. Deaths from lung cancer total approximately 30,000. A mortality ratio of 1.7 for coronary heart disease among cigarette smokers in the seven prospective studies represents from 32.9 percent to 51.7 percent of all excess deaths, whereas the much higher lung cancer mortality ratio of 10.8 from the same studies represents only 13.5 percent to 21.0 percent of total excess deaths (Chapter 8, Tables 19, 25).

PERTINENT PHARMACOLOGY

The acute cardiovascular effects of smoking in man and experimental animals are like those caused by nicotine alone. A smoker who inhales gets usually 1–2 mg of nicotine from a cigarette (56, 57).

Low concentrations of nicotine stimulate sympathetic ganglia, and high concentrations paralyze them. Parasympathetic ganglia respond in the same way but are less sensitive. Nicotine can also have a sympathomimetic effect by causing the discharge of norepinephrine and epinephrine from chromaffin cells in various tissues, including heart, vessels, and skin (9, 10, 11). In addition, nicotine produces effects reflexly by stimulating the chemoreceptors of the carotid and aortic bodies. When nicotine is given intravenously in increasing doses to dogs or cats the first effects, at about 1 microgram/kg body weight, are increased breathing and sympathetic stimulation, with predominant vasoconstriction, cardiac acceleration, and rise in blood pressure, resulting from stimulation of the aortic and carotid bodies (17). Doses of 4 to 8 micrograms/kg can stimulate pulmonary and coronary chemoreflexes which produce opposite effects. If all these receptors are inactivated, much higher doses are needed to evoke the cardiovascular effects of sympathetic stimulation, presumably through action on sympathetic ganglia or chromaffin tissue. Intravenous administration of nicotine in the experimental animal causes a discharge of epinephrine from the adrenal medulla, and in man heavy cigarette smoking produces an increased urinary excretion of catecholamines (84, 99).

Smoking 1–2 cigarettes causes in most persons, both smokers and non-smokers, an increase in resting heart rate of 15–25 beats per minute, a rise in blood pressure of 10–20 mmHg systolic and 5–15 mmHg diastolic (76, 78, 85, 86), and an increase in cardiac output of about 0.5 l/min/sq.m (75). There is a decrease in digital blood flow and a consequent drop in finger and toe temperature (31, 78, 103). The decrease in peripheral blood flow which normally follows smoking does not occur in a sympathectomized limb, indicating that the effect is mediated primarily by the sympathetic nervous system rather than through the release of catecholamines from other sites or the direct effect of nicotine upon the smooth muscle of the blood vessels themselves (103). Intravenous nicotine, and probably cigarette smoking as well, can produce a slight transitory increase in the blood flow to resting calf muscle (79).

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This section on pharmacology of nicotine is so brief that it does not do justice to the considerable amount of information available in 1964. The opening paragraph cites (57) Larson, Haig and Silvette (1961) which is the most extensive monograph on Tobacco. The cardiovascular effects of nicotine are discussed in pages 14 to 232, and the relation of tobacco to cardiovascular disease in pages 653 to 686. However, the monograph is mentioned only in reference to the amount of nicotine absorbed.

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In the dog, nicotine and cigarette smoke cause an increase in coronary flow as the blood pressure, cardiac output, and heart work increase (30, 53). These effects resemble those of epinephrine. Nicotine has been found to cause a transient decrease in cardiac oxygen utilization followed by a slight increase (53). Relatively little information is available about the effect of smoking on coronary blood flow in man. In normal subjects it is reported that cigarette smoking produces an early increase in coronary flow as heart work increases, but there is little change in oxygen utilization by the myocardium (2). With continued "steady state" smoking the coronary flow and cardiac oxygen utilization are maintained at the resting level in both normal subjects and persons with coronary heart disease, despite increased blood pressure, heart rate, and heart work (74). A larger experience must be gathered in this field before statements about the acute effects of smoking on the human coronary circulation can be made with assurance. The atherosclerotic rabbit heart, like the normal rabbit heart, shows an initial drop in coronary flow on administration of nicotine, but demonstrates less of a subsequent increase above the resting level than does the normal heart (97). These effects are said to be equivalent to those produced by norepinephrine in doses one-tenth as large as the nicotine dose.

Little or no change in the electrocardiogram of most normal persons or cardiac patients, except for an increase in rate, is produced by smoking or by the intravenous injection of an equivalent dose of nicotine (82, 93). In some persons there is a slight depression of the S–T segment and a flattening of 1–2 mm in the T wave of the limb leads. These changes are not like those associated with myocardial ischemia. Rarely in persons with true angina, an attack of pain is precipitated by smoking. An ill-defined syndrome consisting of chest pain, palpitation, and shortness of breath, known as "tobacco angina", has been described as occurring in smokers who do not have organic heart disease, but it is rarely diagnosed today (73, 82). Extrasystoles and other cardiac arrhythmias have been reported to be caused by smoking, but such cases appear to be unusual.

The ballistocardiogram obtained from a high-frequency table is sometimes changed by smoking a cigarette from a normal pattern to one said to be typical of coronary disease (78, 91). This phenomenon is rare in healthy persons below 50, becomes increasingly common with advancing years in apparently healthy persons, but is particularly prone to occur at any age in persons with actual coronary disease. The effect has been used as a "stress test" to help uncover coronary disease, but false positive and negative results are common. The ballistocardiographic changes on smoking have been variously interpreted as resulting from impaired myocardial contractility (78), from changes in the peripheral circulation (82), or from uncertain causes related to the physical properties of the high-frequency table as well as changes in the circulation.

Cigarette smoking causes an increase in the concentration of serum-free fatty acids in man (59), apparently mediated by stimulation of the sympathetic nervous system (51). Although continued administration of epinephrine to dogs over many hours can produce substantial increases in serum cholesterol, phospholipids, and triglycerides, such an effect has not yet been reported from nicotine or tobacco smoke (48, 92).

The clotting time of the blood can be decreased 50 percent or more in experimental animals by stimulation of the sympathetic nervous system or by administration of epinephrine (12, 13, 14), but attempts to demonstrate that cigarette smoking alters the clotting properties of the blood in man have been unsuccessful (5, 63). A decrease in platelet survival *in vivo* has been found after smoking (63). Cigarette smokers have been reported to show substantial decreases in hematocrit, hemoglobin, and platelet counts after abstinence of 1–2 weeks (25), but hemoglobin concentrations are alike in smokers and non-smokers of the same population group (64).

Attempts have been made to induce atherosclerosis in rats by the chronic administration of nicotine for periods up to a year without success (93).

Tobacco has antigenic properties (29, 43). Rats can be sensitized to tobacco extracts by intraperitoneal injection. Over a third of smokers demonstrate a positive "immediate" skin reaction to such extracts while only about 10% of non-smokers are said to give positive tests. The presence of serum reagins in persons with positive skin tests has been demonstrated by passive transfer techniques. Persons with thromboangiitis obliterans and smokers with occlusive vascular disease of other types are said to show a much higher incidence of positive skin tests than healthy smokers. The cardiovascular diseases which have been related to smoking, however, do not in general resemble those usually ascribed to an immune mechanism.

In man and experimental animals smoking or the injection of nicotine causes increased secretion of antidiuretic hormone. The renal effects of this are easily demonstrable but the quantity of hormone secreted in response to smoking is probably too small to have significant vascular effects (17).

In summary, the acute cardiovascular effects of smoking and of nicotine closely resemble those of sympathetic stimulation, and to a considerable extent are mediated by excitation of the sympathetic nervous system. No additional or unique cardiovascular effects have been demonstrated which, in the light of our present understanding, seem likely to account for the observed association of cigarette smoking with an increased incidence of coronary disease.

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The information on the effect of smoking on coronary blood flow in man was sufficient to show that there was no harmful influence. The conclusions of (2) Bargeron et al., 1957 and (74) Regan et al., 1961 were similar to those obtained by six groups of investigators administering nicotine in dogs (see page 270). At the time Bargerson et al. and Regan et al. 1961 completed their experiments, their conclusions were accepted because the nitrous oxide technique was the only means of measuring coronary blood flow and myocardial metabolism in man. The observations by Regan et al 1961 have not been disproven by subsequent reports. The Discussion quoted from the article is as follows:

Discussion

The experimental conditions of this stu were limited to evaluation of the sustain effects of cigarette smoking upon the m cardium of man after the peripheral he dynamic changes had become well establish Consequently, interpretation of the data ca not be applied without reservation to t acute changes occurring immediately af the onset of smoking, which may well be qualitatively different.[6] If one assumes, however, that nicotine is the principal pharmacologic agent in tobacco smoke, then the effects of intracoronary infusion of this substance are of some interest. In the intact dog it has not been found to modify coronary blood flow when injected into the anterior descending artery, despite substantial increase in myocardial contractility.[9] Left coronary perfusion with nicotine also has failed to increase flow in the atherosclerotic rabbit heart, despite cardiac acceleration and enhanced contractility.[10] These studies, in which different methods of determining coronary flow have been employed, tend to reduce the possibility that these results in man represent an artifact of the nitrous oxide method.

Augmentation of coronary blood flow may usually be anticipated when there is an increase in heart rate, systemic arterial pressure, cardiac output, and left ventricular work. In this manner, the apparently greater oxygen requirement of the myocardium would be severed. Failure to find such increases of myocardial blood flow and oxygen consumption in the coronary subjects during cigarette smoking may plausibly be related to the "fixed coronary resistance" alleged to exist in such patients.[11] That the abnormal coronary vasculature is not responsible becomes apparent from the similar response in the subjects without evidence of coronary disease. In view of the evidence that ventricular contraction acts to impede coronary flow within the left ventricular wall,[12] the enhanced ventricular contractility as reflected by left heart work may have produced such an effect. This view is difficult to accept, since the failure of coronary flow to meet the need for greater oxygen usage should be associated with augmented oxygen extraction.

Although many of the effects of smoking and nicotine infusion mimic those of catecholamine administration,[5] an evaluation of endogenous catechols in plasma in response to smoking too small to affect the coronary vasculature appears unlikely. On the contrary, small graded doses of catecholamine induce changes in coronary flow before increments in rate and pressure.[13] Another humoral agent possibly released during smoking is antidiuretic hormone.[5] Its potent coronary vasoconstrictor properties raise the possibility that any undesirable effects of smoking could be effected through its activity. Even though the plasma levels of vasopressin probably are not sufficient significantly to restrict coronary blood flow per se, the lack of increased flow despite increments of rate and pressure may represent a restrictive effect of low hormone concentration upon the response to these stimuli of coronary vasodilatation.

It would appear that an enhanced ratio of left ventricular work to oxygen uptake may be maintained for some time without cardiac dysfunction. Such is the case in animals with chronic complete heart block[14] or in those subjected to expansion of intravascular volume.[15] Such disproportion in coronary subjects, however, if large enough, could presumably produce ischemia symptoms. This circumstance, as suggested by this study, would appear to be an uncommon occurrence.[16]

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Tobacco angina. In 1963, Oram and Sowton reviewed the literature and his experiences on tobacco angina. Although the condition is rare, its occurrence has been ignored in prospective and clinical studies of angina pectoris. The subject is discussed in pages 15 to 18. Since the article does not appear in the 1964 or subsequent reports, the summary is reproduced below:

Summary

The term tobacco angina as previously used has become meaningless, and covers at least five separate syndromes to which we have drawn attention. A definition of tobacco angina is offered.

Angina as a result of smoking is a real entity, but rare. Including our three patients, only 17 convincing examples, confirmed electrocardiographically, have been recorded. The commonest type occurs in patients who already have typical Heberden's angina due to coronary disease and precipitated by the more usual causes. A very rare type is that occurring in apparently healthy young people in whom electrocardiographic changes characteristic of coronary insufficiency appear within a few seconds of smoking a cigarette, accompanied or unaccompanied by cardiac pain, but in whom the electrocardiographic changes and pain are said not to be induced by other causes such as exertion, emotion, and cold. We feel it is likely that follow-up studies of these rare patients might later reveal coronary disease.

It is important when searching for patients suffering from tobacco angina to investigate them not only while they are smoking, but after smoking followed by exercise, and after exercise followed by smoking, otherwise examples will be missed. Of 309 smokers with angina questioned concerning the possible role of cigarette smoking in causing cardiac pain, 20 claimed to have angina on smoking. These were re-examined clinically, and electrocardiograms were taken at rest, after smoking, after smoking followed by exercise, and after exercise followed by smoking. Only two examples of genuine tobacco angina were found by this means.

Our three patients had ischaemic heart disease with chest pain, and electrocardiographic evidence of coronary insufficiency was produced by exercise and by smoking cigarettes or cigars. No significant change in blood-pressure accompanied the cardiac pain and electrocardiographic changes which resulted from smoking. These effects induced by smoking were invariably accompanied by tachycardia, but were not secondary to tachycardia as induced by intravenous atropine.

Neither smoking herbal cigarettes nor the intravenous injection of normal saline induced angina or electrocardiographic changes.

The most satisfactory explanation of the cardiac pain and electrocardiographic changes appears to be that nicotine gives rise to coronary insufficiency not by coronary vasoconstriction as previously supposed but by coronary vasodilatation. In spite of this vasodilatation the blood supply to the myocardium becomes insufficient because of the concomitant increase in cardiac work, resulting from an increased cardiac rate, rise in blood-pressure, or both. Possibly also the liberation of catechol amines has a deleterious effect on the metabolism of the myocardium.

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The vasodilatation results from liberation of catechol amines from stores in or near the blood-vessel walls, including the chromaffin tissue along the coronary vessels themselves. Catechol amines cannot be liberated as a result of stimulation of sympathetic ganglia by nicotine, as the blood level of nicotine attained by smoking is too low for this purpose. It is, however, sufficient to liberate catechol amines from blood-vessel walls.

The explanation of the rarity of tobacco angina is not clear. Presumably a few individuals are in some way hypersensitive. The investigation of skin sensitivity to tobacco should be made by using fractionated extracts of tobacco smoke rather than extracts of tobacco itself. We have been unable to demonstrate any sensitivity to either.

To test the theory that release of catechol amines by nicotine leads to tobacco angina, we tried six drugs which might be expected to block the nicotine effect, and four which might be expected to aggravate it. The former group consisted of dihydroergotamine, antiserotonin, reserpine, hydrocortisone, guanethidine, and methyl dopa, while the latter comprised serotonin and three monoamine oxidase inhibitors. The results are given in detail. Surprisingly, the monoamine oxidase inhibitors had a protective effect in all three patients. None of these drugs blocked the effect of exercise.

Our results support the belief, previously based on animal experiments, that nicotine exerts an action like that of the sympathetic stimulants because it liberates noradrenaline.

If it is thought by the patient that his angina is induced more easily during the time he is smoking, he should be persuaded to abstain for one month, and the electrocardiogram should then be repeated. If clinical improvement is reported and the height of the T wave has also improved, he should be permanently discouraged from smoking.

Indiscriminate advice against smoking, as far as angina is concerned, is not justified, and each patient needs individual assessment.

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GENERAL OBSERVATIONS ON CORONARY HEART DISEASE

Heart disease is the most common cause of death in our population, and coronary disease is the commonest variety of fatal heart disease (59). In 1961 there were 1,501,522 deaths from all causes in the United States. Heart disease deaths numbered 663,391 of which 502,351 were due to arteriosclerotic heart disease.

The disorder consists of obstruction or narrowing of the coronary arteries, reducing the blood supply to the heart muscle. The underlying cause of the obstruction is coronary atherosclerosis, but an acute coronary artery occlusion is often caused by the formation of a blood clot in a diseased artery. The common manifestations of coronary disease are angina pectoris, recurrent brief attacks of chest pain caused by inadequate blood supply to the heart muscle; myocardial infarction, or necrosis of a portion of the heart muscle due to acute loss of blood supply; congestive heart failure, a chronic state caused by inability of the heart to pump enough blood to satisfy the demands of the body; and sudden death resulting from cardiac standstill or ventricular fibrillation.

There are considerable differences in the prevalence of coronary heart disease in different countries, and often in different ethnic and socio-economic groups within a particular country (49, 62). The reported death rate of arteriosclerotic heart disease, which is primarily coronary disease, is higher in the United States than in other countries. It is also quite high in New Zealand, Australia, South Africa, Canada, and Finland, and moderately high in Great Britain. The death rate in Norway, Sweden, and Denmark is roughly half that in the high death rate countries (65). The death rate in Japan appears to be about one-sixth that in the United States, although persons of Japanese origin living in the United States are said to have a death rate similar to that of the general population of this country (52).

Because of changing diagnostic skills and revisions in nomenclature of disease, it is difficult to be certain of the change in incidence of coronary disease in the United States over the past few decades, but there is a general opinion that the incidence is increasing in this country and in England, particularly in the younger male group (59, 62, 65, 83). In 1955 the mortality rate from arteriosclerotic heart disease was reported to be about 240 per 100,000. Although this is an increase of more than 50% over the rate in 1940, it has been estimated that less than 15% of the increase represented a real change in incidence of the disease, the remainder depending upon changes in diagnosis, in nomenclature and in the age of the population (59). Since 1955 the death rate from coronary disease (ISC 420) and from arteriosclerotic and degenerative heart disease (ISC 420 and 422) has continued to increase gradually. In 1960 the age-adjusted death rate from 420 and 422 was 336 per 100,000 for white males and 160 for white females (55).

Although the basic cause or causes of coronary heart disease are obscure, certain factors other than smoking are known or thought to predispose to the condition or to be associated with an increased incidence.

The incidence of coronary heart disease in men under 45 is about 5 times as great as that in women (Table 1) (15, 20, 59, 62). In both sexes the incidence increases with advancing years. After the menopause the incidence increases rapidly in women, and at age 80 the death rates from coronary disease are about the same for the two sexes. Coronary thrombosis plays a relatively more important role in precipitating myocardial infarction in young men than it does in old men (105). In studies of large population groups coronary disease has been associated with elevation of the serum cholesterol, hypertension, and marked overweight (19, 20, 24, 36, 45, 59, 62).

Some individual characteristics have been said to be associated with coronary disease. There is a significant familial tendency to develop it (36, 69, 81, 96). Persons with a mesomorphic constitution are said to be more vulnerable than endomorphs and ectomorphs (59, 62, 83). A coronary-prone personality has been described as the aggressive, competitive person who takes on too many jobs, fights deadlines, and is obsessed by the lack of adequate time for the performance of his work (33, 34, 35).

TABLE 1.—*Death rates per 100,000 from arteriosclerotic and degenerative heart disease* by sex and age, United States, 1958–60*

Age Group	Males	Females	Both Sexes
Under 35	3.3	1.2	2.2
35–44	90.2	18.3	53.3
45–54	353.7	79.8	213.5
55–64	928.5	314.5	610.2
65–74	2129.2	1062.0	1569.5
75 or over	4765.1	3738.4	4179.7

*Includes ISC numbers 420 and 422.

Source: WHO Epidemiological and Vital Statistics Report, Vol. 16, No. 2, 1963 (15).

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Some of the articles cited in this page discuss the interrelationship between smoking and other risk factors. One example is (81) Russek and Zohman, who described hereditary predisposition as well as other risk factors in coronary heart disease of young adults. Although smoking was prevalent in the coronary group, it appeared to the authors to be an indication of heightened emotional tension rather than a predisposing or causative factor in coronary heart disease.

TOBACCO. Prior to the attack, 90% of the coronary patients indulged regularly in the use of tobacco, while 10% were either nonsmokers or participated on rare occasions. Among controls, on the other hand, 62% were habituated while 38% smoked occasionally or not at all. Heavy smokers were also found to be far more frequent in the coronary group. Thus, 70% of their number had smoked at least 30 cigarets per day prior to their attack as compared with only 35% in the contratest group. These observations indicate, therefore, that smoking was not only more prevalent in the coronary group but also that the coronary patients who had smoked were more heavily addicted to the use of tobacco. Nevertheless, it is not clear from these findings whether nicotine is a predisposing factor in coronary heart disease or whether its more frequent and excessive use among young candidates is merely a reflection of the heightened emotional tension so prevalent among them.

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Certain occupations have been said particularly to favor the development of coronary disease, notably those which feature responsibility and stress (34, 81, 87), and which are sedentary in nature (71). Others (33, 72, 90) have not found that executives are more prone to coronary disease than non-executive personnel. Physicians have been said to have 3 or 4 times as much coronary disease as farmers or laborers (87), and general practitioners to have 3 times as much as dermatologists (56). Occupations involving much physical activity are said to be protective (16, 67, 77). City life has been said to be more closely associated with coronary disease than suburban life, and men who drove more than 12,000 miles a year seemed, in one study, more prone to the disease than those who drove less (64).

It has been widely held, and occasionally denied, that a diet high in saturated fat predisposes to the development of coronary disease (40, 52, 69, 81). A correlation between the national incidence of coronary disease and the percentage of food calories available as saturated fat has been reported among those countries for which adequate data exist (56). The serum cholesterol tends to rise when saturated fat is added to the diet, and it falls significantly when unsaturated fat is substituted (61). It has also been suggested that general over-nutrition, rather than excess saturated fat predisposes to coronary disease, on the grounds that the correlation of coronary disease with total available calories or sugar consumption per capita is as good as that for percentage of calories in fat (106).

In general, it is apparent that multiple personal and environmental factors can markedly affect the incidence of coronary disease.

SMOKING AND CORONARY HEART DISEASE

Over the last two decades a considerable number of epidemiologic studies on different populations, employing different techniques, have shown with remarkable consistency a significant relationship between cigarette smoking and an increased death rate from coronary heart disease in males, particularly during middle life. There has been little dissenting evidence. The association of coronary disease with the use of tobacco in other forms has not been striking. The documentation for these statements is given in the following paragraphs. Particularly important is the information in Chapter 8, Mortality.

English et al. (26) found the incidence of coronary disease in male patients at the Mayo Clinic about 3 times greater in cigarette smokers than in non-smokers in the 40–59 year age range, but found little relation to smoking above (6). Russek (61) reported a similar relationship, but less striking, in young men with coronary disease. Mills (64) in a study of reported mortality in a Cincinnati population found that heavy smokers in the 30–59 year age range had twice as high a death rate from coronary disease as non-smokers. Male Seventh Day Adventists, who are non-smokers, were found by Wynder and Lemon (104) in a study based on hospital admissions to have significantly less coronary disease and to develop it later in life than the general male hospital population. Haag and Hanmer (37) reported that employees in the tobacco industry, who tend to smoke heavily, had a lower death rate for cardiovascular disease than the general population in their geographic region, but no report was made of mortality rates within the tobacco-worker group, divided by smoking habits. The study has been criticized on this and other grounds (16).

Large-scale prospective studies of mortality in British physicians (Doll and Hill, 21), United States males 50–69 recruited by volunteer workers (Hammond and Horn, 38, 39, 40, 42) and V.A. Life Insurance policyholders (Dorn, 22) have confirmed the association of death from coronary disease with cigarette smoking. In the British study, a step-wise association was found between the amount of tobacco consumed (not entirely cigarettes) and the mortality from coronary disease. The association occurred in the 35–54 year age range, but not in older men. Hammond and Horn found a similar graded relation-ship between coronary deaths and cigarette smoking, the death rate being more than twice as great in men who smoked over a pack a day as in non-smokers. Men who had stopped smoking for more than a year at the start of the study had a coronary death rate lower than those who continued.

Studies on special groups of men, such as longshoremen (Buechley et al. 8) members of a fraternal order (Spain and Nathan, 69) and industrial employees (Paul et al. 71) which, in the latter two instances, incorporated clinical coronary disease, as well as coronary deaths, also have shown a relation-ship between coronary disease and smoking. The relationship was closer for men under 55 than for older men, and closer for myocardial infarcts and death than for angina pectoris (70, 69).

The long-term prospective studies of cardiovascular disease in Framingham (19) and in Albany (23) which have features of painstaking search at regular intervals for clinical manifestations of disease, have, on pooling the data (Doyle et al. 23) shown a three-fold increase in the incidence of myocardial infarction and coronary deaths in men who are heavy cigarette smokers as compared to non smokers, pipe and cigar smokers, and former cigarette smokers. In the pooled data the incidence of angina pectoris did not show a significant association with cigarette smoking. The lack of this particular relationship had been suggested on the basis of clinical experience (White and Sharber, 102).

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When selected groups are examined, there is no relationship between cigarette smoking and an increased death rate from coronary heart disease. The report by Cohen and Heimann (1962) is a good example. It is reproduced in its entirety.

Cohen J and Heimann R K: Heavy smokers with low mortality. Ind Med Surg 31: 115-120, 1962.

This paper extends mortality rates of cigarette division employees of The American Tobacco Company to cover the period 1957-1960. Previous mortality studies of the same population were made by Dorn and Baum of the National Institutes of Health, embracing October, 1946, through 1952,[1] and by Haag and Hanmer, for the years 1953 through 1956.[2] An intensive investigation of this population's smoking habits was made in 1956 by Finkner et al.[3] of the Institute of Statistics of the University of North Carolina.

The 1957-1960 data confirm the findings of Dorn-Baum and Haag-Hanmer that the age-, color-, and sex-adjusted mortality rate for all causes, for cancer, for respiratory cancer, and for cardiovascular disease in this population are average or lower than average when compared with the general population rates.

The significance of this finding relates to the determinations of Finkner et al.,[3] who found that the population under study had a markedly higher percentage of regular cigarette smokers than the general U. S. population. Finkner's study also indicated that the percentage of these factory employees consuming upwards of 20 cigarettes daily was twice that in the general population.

This series of studies thus establishes a distinctly heavier-than-average smoking population which has, over a period of 14¼ years, manifested fewer deaths of all kinds, and fewer deaths from cancer, lung cancer, and heart disease, than the expectancy for an average population of its age, sex, and racial composition. These results are in direct opposition to the hypothesis that cigarette smoking per se causes higher mortality rates generally and for lung cancer and/or heart disease.

The three consecutive longevity investigations covered 70,532, 45,455 and 41,967 person-years respectively, or a total of 157,954. The average size of the population during the 171 months under study was slightly over 11,000.

Mortality Rates for 1957 through 1960

Table I compares the observed deaths in the population studied with the expected number based on age-sex-color-specific death rates for the general U. S. population. This table and the method of its calculation are patterned after those published by Dorn-Baum and Haag-Hanmer.

TABLE I.
OBSERVED AND EXPECTED NUMBER OF DEATHS FROM SPECIFIED CAUSES AMONG FULL-TIME AND RETIRED EMPLOYEES OF CIGARETTE PLANTS AND STEMMERIES OF THE AMERICAN TOBACCO COMPANY
JANUARY 1957 — DECEMBER 1960

Cause	Expected No. of Deaths	Observed No. of Deaths	Observed to Expected
All causes	425	325	76%
Cancer — all forms (140-205)	75	47	63%
Cancer — respiratory system (160-164)	14	6	43%
Cancer of bronchus and trachea, and of lung specified as primary (162)	7	0	0
Cardiovascular (400-468)	180	154	86%
Coronary disease (420)	116	100	86%

NOTE: Numbers in parentheses are cause-of-death categories of Seventh Revision of The International List, as used in *Vital Statistics of The U. S.*

Dr. Cohen is also consultant to the Department of Research and Development of the American Tobacco Company.

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Table I indicates that the observed number of deaths during the 1957-1960 period was 76% of the number that would be expected to occur in an average U. S. population similarly stratified as to age, sex, and color. The number of cancer deaths was 63% of the expectancy. Respiratory cancer deaths were 43% of the expectancy, cardiovascular deaths 86% of the expectancy, and coronary deaths 86% of the expectancy. No deaths from primary lung cancer occurred during this period, although an expectancy of seven such deaths was derived from vital statistics for the U. S. as a whole.

Previous Mortality Rates for the Same Population

Similar percentages of observed-to-expected deaths in the several classifications were observed by Dorn-Baum for the period October 1946-1952 and by Haag-Hanmer for 1953-1956. Percentages of observed-to-expected deaths covering the results of all three studies as well as the complete time span of 14¼ years are arrayed in Table II. Allowing for the random fluctuation in the number of particular causes of death that is observed in most population subgroups, and especially for those causes from which the number of deaths is small (e.g., respiratory cancer), the results of the three investigations show internal consistency. Except for the aforementioned cause involving few deaths, the percentages from one study to the next show no radical variation. The over-all percentages in Column 4, Table II, characterizing the observed-to-expected ratio for the several cause categories during the entire 14¼ year period, fall within a range of nine percentage points. Observed deaths ranged from 70% to 79% of the expectancy for all causes, for cancer, for respiratory cancer, for cardiovascular and for coronary disease.

Since Dorn-Baum did not compute a separate expectancy category for primary lung cancer as distinct from the general category of respiratory cancer both primary and secondary, this category does not appear in Table II. In the two latter studies covering eight years, four deaths from this cause were recorded, representing 36% of the normal expectancy of 11.

TABLE II.
PERCENTAGE OF OBSERVED TO EXPECTED DEATHS IN THREE SUCCESSIVE STUDIES OF FULL-TIME AND RETIRED EMPLOYEES OF CIGARETTE PLANTS AND STEMMERIES OF THE AMERICAN TOBACCO COMPANY

	Dorn-Baum (Oct. 1946-1952)	Haag-Hanmer (1953-1956)	(1957-1960)	Total Period (Oct. 1946-1960)
All causes	88%	69%	76%	71%
Cancer - all forms	73%	77%	63%	70%
Cancer - respiratory system	86%	100%	43%	71%
Cardiovascular	65%	76%	86%	75%
Coronary disease	80%	65%	86%	79%

Smoking Habits of the Population under Study

As previously reported by Finkner et al., the proportion of regular cigarette smokers among the tobacco employees studied was much greater than that in the general U. S. population. Among white males, 77.2% of the tobacco employees were regular cigarette smokers, compared with 49.9% for the general U. S. population; for nonwhite males, 84.1% compared with 48.4%; for white females, 44.4% compared with 23.6%; and for nonwhite females, 61.7% compared with 22.9%.

The tobacco employee population also included a considerably higher percentage of smokers consuming more than 20 cigarettes daily than the general U. S. population. Among white males, 32.8% of the tobacco employees smoked more than 20 cigarettes a day as against 13.3% for the general U. S. population. Nonwhite males among the tobacco employees included 16.5% smoking more than 20 cigarettes a day as against 6.9% in the general U. S. population. For white females the proportion was 6.9% among tobacco employees as against 2.1% in the general population, and for nonwhite females 4.0% as against 1.7%. In each category, the proportion of tobacco workers smoking more than 20 cigarettes a day is of the order of two and a half times that of the comparable segment of the U. S. population.

Methodology

In all three mortality studies, observed deaths were tabulated from reports of the Metropolitan Life Insurance Company, which underwrites insurance policies on all employees of the group studied, including those on leave, those retired for disability, and those retired for age. Death rates for the general U. S. population were computed by dividing total deaths, as reported in *Vital Statistics of the U. S., Volume II*,[4] by the population estimates issued by the Bureau of the Census for July 1 of each year (Series P-25).[5]

For the 1957-1960 period, rates for the year 1958 were used to compute expectancies for 1957 and 1958, and rates for the year 1959 were used to compute expectancies for 1959 and 1960. Rates were computed separately for male white, male nonwhite, female white, and female nonwhite, and for all the age groups 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75 and over. These rates were applied to the number of person-years of exposure in each age, color, and sex category of the population under study. The roster of employees (including retired employees and those

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on leave) was taken as of July 1 in each year. Expectancies throughout were calculated for each single year and summed for the period studied.

Measurement of the subject population's smoking habits by Finkner et al. was methodologically similar. Independent investigators recorded individual smoking histories and classified them by age, sex, color, and rate of cigarette consumption. These were ranged against the corresponding findings for the general population of the U. S. by subgroup, as reported by Haenszel, Shimkin, and Miller of the U. S. Department of Health, Education and Welfare,[6] based on a Census Bureau study.

The above procedure follows that of Haag and Hanmer, who compared employee smoking habits with those of the U. S. population, and employee mortality rates with those of the U. S. population, both stratified by age, sex, and color.

No sampling or estimating was involved in any of these studies. Smoking habits were measured by applying pretested procedures individually to virtually every member of the population under study (98.1%). Data on age, color, sex, and mortality were available for each individual member of the population and were summed as above described.

Characteristics of the Population

The population under study was that defined by Dorn and Baum of the National Institutes of Health. It consists of full-time employees in factories and leaf departments of The American Tobacco Company in Virginia, North Carolina, and Kentucky. Turnover in this employee group is negligible. On July 1, 1960, approximately 66% of the population had service records of ten years or more, and 20% had service records of 25 years or more. On August 1, 1953, 48% had been employed ten or more years, and 10%, 25 or more years.

As reported by Dorn and Baum, employees who are unable to work eventually are carried on the payroll as on leave without pay but remain covered by insurance so that they remain part of the population for purposes of these studies. Retired employees retain insurance coverage and also are included.

Thus the population is a coherent group for purposes of mortality investigation. The degree of this coherence is indicated by its average age, which increased almost precisely three years between July 1, 1957, and July 1, 1960 — from 42.8 years to 45.7 years, respectively.

White males accounted for 43% to 46% of the population during this period, these percentages being minimum and maximum. Males white and nonwhite accounted for 57% to 61% of the subject population. Men over 45 accounted for 31% of the employee group on July 1, 1960.

Comment

The health history of this population of heavy-smoking tobacco company employees tends to disprove the hypothesis that cigarette smoking causes higher mortality from all causes, from cancer, from lung cancer, or from heart disease. This interpretation is strengthened by the following data of observation:

1. The substantial degree to which the studied population's cigarette consumption exceeds the national average: In the percentage smoking more than 20 cigarettes daily, the Finkner study group recorded the ratio as 2:1 or more in every subgroup and in virtually every age group. In view of the population's vocational interest in the product it manufactures, and the provision of a free package of cigarettes each working day, this characteristic of the group studied is not astonishing.

2. The unusually stable nature of this employee group, as indicated under "Characteristics of the Population" above: Stability of the population for purposes of these studies is also insured by the fact that employees on leave, retired for disability, or retired for age, continue to be covered under the group insurance plan. These employees or former employees were included on the July 1 rosters used to compute expected deaths; and actual deaths among them were reported by the Metropolitan Life Insurance Company.

3. The extended nature of the mortality research, covering a continuous time span of 14¼ years.

4. The consistently lower-than-average mortality of the studied population for each of the three mortality studies (Table II).

5. The consistency of the degree to which this mortality for the entire 14¼ year period is lower than the national rate, as between the various causes of deaths (Table II, Column 4).

Other Statistical Studies

A number of studies, of which those of Doll-Hill[7] and Hammond-Horn[8] are representative, have yielded a statistical association in individuals between cigarette smoking and higher mortality rates. Other studies, including Eastcott, Dean, and the present study, have shown no such association. A number of distinctions may be noted in connection with the diametric opposition between the results of the two groups of studies.

Statistical association studies of the Ham-

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mond-Horn, Doll-Hill type compute expected deaths on the basis of mortality rates shown by professed nonsmokers. The professed nonsmoker is taken as the norm or "average" against which various types of smokers are compared. This raises two questions: (1) whether those smokers who manifest higher mortality rates do so as a direct result of the effects of smoking, or whether the smoking habits of some of these higher-mortality smokers are diagnostic of other factors that predispose to shorter life, and (2) whether the professed nonsmoker with his low mortality rate can be taken as a norm.

The former question cannot be answered from the statistics themselves, since this would require that all relevant or predisposing factors other than smoking be held constant. No attempt was made in the Doll-Hill, Hammond-Horn, or their counterpart studies to do this, since all relevant factors affecting mortality and or cancer mortality are not known, and since some of the suspected factors — previous medical history, genotypic differences, constitutional predisposition, exposure to various environmental agents, "rate of living," the "stress" factor, etc. — are difficult if not impossible to reduce to mathematical terms, even if they could be gathered for populations large enough for statistical study.

Touching on the latter question, Berkson[9] has noted that

> . . . persons who are nonsmokers, or relatively light smokers, are of a constitutional type that is biologically disposed to self-protective habits. . . . It is not implausible that they should be, on the average, relatively longevous, and this implies that the death rates generally in this segment of the population will be relatively low.

The extent of this difference between death rates of professed nonsmokers and average U. S. citizens was indicated by Hammond-Horn, who computed mortality rates of 777, 1,253, 1,781, and 3,280 per 100,000 for nonsmoking white males in their 50-54, 55-59, 60-64 and 65-69 age groups, compared with rates of 1,469, 2,210, 3,402, and 4,895 per 100,000 for white males of the same age groups in the general population. These mortality differences between the professed nonsmoker and the "average" white male reported by Hammond-Horn were great — 85%, 76%, 91%, and 49%. Should Berkson's characterization of nonsmokers be correct even for a number of persons in that category, the Hammond-Horn interpretation that cigarette smokers incur "excess" mortality rates becomes meaningless. That is, the association their data showed reflects only the choice of an abnormally longevous group as a criterion of what is "normal." The same would be true of a number of other statistical association studies patterned on the Doll-Hill model.

The influence of this choice of criterion on their final calculations is evident from Hammond-Horn's own comparison of death rates among their "heavy cigarette smokers" with death rates among U. S. white males generally. In a 20-month period these rates were 1,222; 2,140; 2,707; and 3,856 per 100,000 for "heavy cigarette smokers" against 1,288; 2,096; 2,991; and 4,354 per 100,000 for U. S. white males in the four age groups. These rates hardly differ. In a subsequent 24-month period the "heavy cigarette smokers" showed slightly higher death rates than the U. S. average.

Apart from the question whether nonsmokers constitute a valid criterion of "normal" mortality — and Hammond-Horn's figures strikingly suggest they do not — a basic difference exists between the two types of studies mentioned. Those patterned after the Doll-Hill model (including Hammond-Horn) attempt a correlation between mortality rates and smoking habits in individuals. This requires the assumption that no unmeasured other factors exist that might account for or explain any correlation that is found. The number of such factors investigated, alone or in conjunction with smoking habits, is thus far small — the so-called "urban factor" (assumed by some to be air pollution), certain special occupational exposures, and alcohol consumption.

By contrast, studies of population subgroups including this series, those by Eastcott,[10] and that by Dean,[11] deal with mortality rates and smoking habits of groups. Dean compared native white male South Africans with British male immigrants to South Africa 45-64 years of age. Between 1947 and 1956 the death rate from lung cancer among the former was 50 per 100,000, and among the latter, 112. At the same time, white South Africans are among the world's heaviest cigarette consumers, with a per capita usage reported 68% above that in the United Kingdom in 1950 and 40% higher than the U. K. figure in 1955. Dean found urban residence to correlate with lung cancer incidence among South African whites, and concluded that "bronchial carcinoma must result from the total effect of genetic and environmental factors."*

*Dean later gathered smoking habit data for about half the lung cancer deaths in his study. Using these and a set of matched "controls" — deaths from other causes — he estimated mortality rates by age groups, by country of origin, by rural-urban residence, by occupational air pollution, and by rate of smoking.

The greatest relative association with lung cancer in these estimates involved country of origin (U.K. vs. Union of South Africa), but urban residence also showed consistent association. Occupation showed no association. As to smoking, rural South

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Eastcott found a parallel difference in lung cancer mortality between immigrants from Great Britain to New Zealand and native-born New Zealanders; at the same time tobacco consumption for the two groups was observed to be comparable. Eastcott concluded that "Differences in habits of tobacco-smoking are unlikely to contribute to this picture," and "The environmental factors concerned are unlikely too to be of a personal kind related to the way of life of the immigrant." In 1960, his data were extended to cover ten years' comparison of the mortality experience of 250,000 immigrants from the U. K. against that of 2,800,000 native-born New Zealanders.

Neither Dean nor Eastcott nor the present study offers a correlation between a single factor and mortality rates. They merely indicate that the higher mortality, whether from lung cancer alone or from this and other causes, does not associate with higher tobacco consumption. Rigorous interpretation of these findings as opposing the tobacco theory does not require the assumption that other factors remained constant. Actually, the results indicated that other factors did not remain constant, since important death rate differences were recorded despite similar or contrahypothetical rates of smoking, although the precise identification of these other factors is not germane to this inquiry.

Bearing on both types of study is the observed tendency of many selected population subgroups to manifest lower mortality rates than the population as a whole. Hammond-Horn, for example, estimated that "the death rate of our study population would stabilize at about 81% to 85% of the rate for white males in the general United States population," attributing this favorable comparison to selection of subjects from counties with lower death rates and to "a slight degree of socioeconomic selection."

Employee populations, such as the one studied by Dorn-Baum, Haag-Hammer and the writers, also represent a degree of selection resulting from the initial medical "screening" of applicants for employment. This effect, according to Hammond-Horn, "diminishes rapidly with time, is relatively slight after the third year, and for all practical purposes wears off within five years." Although the exact duration of this screening effect would not be important in a study extending 14¼ years, the significance of the present study does not lie in the fact that the tobacco employee population (like other selected groups) shows lower-than-average mortality. Rather, it lies in the fact that this lower-than-average mortality exists concurrent with a pattern of distinctly heavy smoking and in the fact that respiratory cancer mortality — alleged to be specifically and causally linked to cigarette consumption — is as much below average in this heavy-smoking population as is mortality from other causes or from all causes.

It has been pointed out that employee groups enjoy better-than-average medical care and for this reason are likely to manifest lower-than-average mortality rates. In the first mortality study in this series, Dorn-Baum noted the findings "are not surprising in view of the medical care program provided by the company for its employees."[1] To the extent that medical care favorably affects the mortality rates of the employee population, the postulate is denied that cigarette smoking in and of itself is a major cause of respiratory cancer, or heart disease, or decreased longevity.

The previous study in this series[2] was criticized on several grounds by Case[14] who, in turn, was quoted by Cornfield et al.[15] This criticism if valid, also would apply to the present report:

1. Case questions the comparability of the tobacco workers with the general population in regard to characteristics other than smoking (and age-sex-color, which is allowed for in the determination of expected rates). On grounds such as these all statistical studies in this area may be called into question, but the present study less than most, since it represents a cross-sectional population with regard to socioeconomic-occupational levels. Further, the basis of Case's argument, that mortality, particularly from primary lung cancer, is associated with *other* factors, calls into question the specificity of the tobacco hypothesis.

2. Case applies a Hammond-Horn factor for increased lung cancer mortality expectation (based on the tobacco workers' greater smoking rate) of 1.7 to the previous study and arrives at an expected number of lung cancer deaths of seven. He then demonstrates that the sampling error of this study is such that 0-8 such deaths could occur at the $P = .05$ level, and that since this includes the adjusted frequency of seven, the results cannot refute the

African-born men smoking 1-20 cigarettes a day showed lower lung cancer mortality rates than nonsmokers in such U.K. locations as Liverpool, Lancashire, Dewsbury S.E., Flint and Cheshire. Also, "In South African rural areas the lung cancer mortality rate for men aged 45 to 84 years was very low for both nonsmokers and moderate smokers, and increased only with heavy cigarette smoking," and "The highest lung cancer mortality rates were found where heavy smoking was combined with exposure to air pollution." (*Brit. Med. J.* 2:1599, 1961).

Dean's estimates suggest the possibility that excessive smoking may be diagnostic of other factors predisposing to higher mortality rates; this could account for the associations found by Doll-Hill and Kreezer and would also be compatible with the finding of low mortality rates for large groups of smokers in Dean, Eastcott, and the present study.

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Hammond-Horn tobacco hypothesis. Using exactly this reasoning on the cumulative 1953-1960 results, the expected frequency is 11 (four in 1953-1956 and seven in the current period), the .05 confidence interval is $11 \pm 2\sqrt{11}$ which provides a range of 4.4 to 17.6. Applying the Hammond-Horn factor of 1.7 to the expected value of 11 results in a hypothetical expectancy of 18.7 lung cancer deaths, a value that falls outside and above range of the confidence interval. Although the writers have serious reservations about the procedure suggested by Case, its application to the extended series results in a rejection of the Hammond-Horn tobacco hypothesis.

3. The additional points made by Case are hypothetical ones regarding the possible unrepresentativeness of the population and shortness of the period studied. Data with regard to some of these issues were lacking in the Haag and Hammer[2] report, but have been included above. They indicate that the representativeness of this population, and the length of time over which relevant data have now been gathered, cannot be called into serious question.

Summary

This study extends to 14¼ years mortality data of approximately 11,000 employees of cigarette factories and stemmeries in Richmond, Virginia; Durham and Reidsville, North Carolina; Louisville, Kentucky; and other locations. It confirms the findings of previous studies that this population shows lower mortality rates for all causes, for cancer, for respiratory cancer, for heart and coronary disease, than the expectancy for a population of its age, sex, and color composition based on mortality rates of the U. S. population in general. For the full period studied, the degree to which its mortality is lower than average is similar for all death causes mentioned. Independent measurement has indicated that the subject population includes more than twice as many more than 20-per-day cigarette smokers as the percentage in the general U. S. population. These findings, obtained without recourse to sampling or estimates, are contradictory to the hypothesis that cigarette smoking per se is causally related to increased mortality, from all causes, from respiratory tract cancer, or from heart disease.

The low turnover of this employee group, and the inclusion of retired and disabled personnel on the insurance rosters make this a relatively stable population suitable for an extended mortality study. The margin by which its cigarette consumption exceeds the U. S. average makes it further suited to a test of the cigarette theory.

Analysis of statistical association studies on which the cigarette theory is largely based indicates certain assumptions and criteria as to "normal" death rates which influence the final calculations of these studies. The validity of these assumptions and criteria is called into question by the results of this and other studies that do not confirm the cigarette theory.

The negative findings of these data with respect to the cigarette theory parallel and confirm the negative findings of other extended tests of the same hypothesis: that of Eastcott, who studied cancer mortality of the entire census population of New Zealand and of immigrants of similar stock from the U. K. over a 10-year period; and that of Dean, who studied lung cancer mortality among male white native South Africans and male white immigrants from the U. K. to South Africa, also over a 10-year period.

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An apparent interplay of factors relating to smoking and occupation turned up in a short-term study of the development of coronary heart disease in a general North Dakota population (Zukel et al., 1071). Farmers had about half the incidence of myocardial infarction experienced by others. In farmers, smoking had no appreciable effect on the incidence of infarction, but in others the incidence of infarction was twice as high among smokers as among the non-smokers. The farmers who smoked cigarettes smoked less heavily than males in other occupational groups.

In Chapter 5, Mortality, there is summarized the most recent information available from 7 large completed or current prospective smoking and death rate studies (Doll and Hill; Hammond and Horn; Dorn; Dunn, Linden and Breslow; Dunn, Cutil and Breslow; Best, Josie, and Walker; and Hammond). The median mortality ratio for coronary disease of current cigarette smokers to non-smokers is 1.7 (range 1.5–2.0).

Table 2 presents data from some of the large prospective studies on the ratio of mortality rates due to coronary heart disease of male smokers to non-smokers, by age and amount smoked. The ratios tend in general to increase with amount smoked and to decrease with advancing age.

The data from the first 22 months of Hammond's (41) current study help to show the size of the coronary problem. For this purpose, actual numbers of deaths may be more informative than mortality ratios. Of nearly

TABLE 2.—*Ratios of mortality rates for coronary heart disease, male smokers to non-smokers, by age and amount smoked, in selected studies*

HAMMOND AND HORN—1958 (42)

Age Group	Cigarettes smoked per day		
	Less than 10	10–19	20 and over
50–54	1.4	2.0	2.3
55–59	1.4	2.0	2.3
60–64	1.3	1.9	1.9
65–69	1.2	1.6	1.6
Total (age adjusted)	1.29	1.83	(20–39) 2.15 | (40+) 2.01

BERCHELEY, DRAKE, BRESLOW—1958 (8)*

35–44		2.6
45–54		2.5
55–64		1.8
65–74		0.9

FRAMINGHAM STUDY—1962 (47)

30–62	(less than 20) 1.5	(20 and over) 2.2

DORN—1958 (22)

Total (age adjusted)	1.22	1.76	1.75

DOLL AND HILL—1956 (21)

Age Group	Grams of tobacco smoked per day		
	1–14 Grams	15–24 Grams	25 or more Grams
35–54	2.2	3.3	4.2
55–64	0.9	0.8	1.0
65–74	1.0	0.9	1.3
75+	1.3	1.0	1.6
Total (age adjusted)	1.1	1.1	1.4

*Persons smoking 1 pack per day or more compared with those smoking less than 1 pack per day (including non-smokers).

10,000 deaths of men aged 45–79, 46 percent were ascribed to coronary disease. 51.7 percent of the 2,630 "excess deaths" associated with cigarette smoking were caused by coronary disease. In approximate terms, nearly half of middle-aged and elderly males in the United States die of coronary disease. About half of these males smoke cigarettes. Cigarette smokers have been found in several studies to have 1.7 times as high a coronary death rate as non-smokers. If cigarettes actually caused the additional coronary deaths of smokers, they would account for many deaths of middle-aged and elderly males in this country. Like other studies (19, 21, 22, 23, 42) this one shows that the ratio of smokers' coronary death rates to those of non-smokers increases progressively with the daily cigarette consumption. In addition, at each level of consumption the ratio increases with the amount of inhalation reported by the smokers. Others (21, 23, 26, 50) have indicated that the risk of death from coronary disease in male cigarette smokers relative to that in non-smokers is greater in middle age than old age, and Hammond's current study supports this. The mortality ratio was 3.09 in the age range 40–49, and in successive decades was 2.20, 1.55, and 1.20.

Men who stop smoking have a lower death rate from coronary disease than those who continue (21, 42, 47). In the study of Hammond and Horn (42) the decrease in death appeared only after a year.

Angina pectoris is less closely related to cigarette smoking than myocardial infarction and sudden death. In the combined Albany-Framingham experience (23), angina pectoris showed no overall relationship with smoking, and the association has not been strong in other studies (51, 59).

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The statistical method used in the prospective studies have been reviewed by Brownlee (Am Stat Assoc J 60: 722-738, 1965). This article is so important that it is reproduced in its entirety.

A REVIEW OF "SMOKING AND HEALTH"*†

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ALTHOUGH there were earlier papers in the medical literature, e.g. Müller [1], the possibility of an association between cigarette smoking and lung cancer first became common knowledge among statisticians generally with Doll and Hill's [2] retrospective paper published in 1952. A retrospective study is one in which a group of, e.g., cancer patients is classified by their smoking habits, and a second group, the controls, known to not have cancer, but sampled from the same population as the cancer patients, is also classified by their smoking habits. The resulting 2×2 table, in which in principle the two sample sizes are fixed, can be tested for independence. The evidence for the association became more convincing with the publication in 1954 of two reports on prospective studies, one in England by Doll and Hill [3] and one in the United States by Hammond and Horn [4]. In a prospective study, a population is sampled and then each individual is classified by, e.g., his smoking habits and by his experience with respect to cancer after an interval of time sufficient to allow a reasonable number of cases of the disease to develop.

I have observed amongst some statisticians a wistfulness that statistics has not so far played a larger part in science generally. Since this association between smoking and lung cancer, interpreted by many as one of causation, is of prime importance, one might have expected it to be greeted with enthusiasm and loud admiration. On the contrary, the comments and reactions of the statistical profession have been very restrained. By and large, in fact, the silence has been deafening.

In 1955, Neyman [5] pointed out a possible fallacy in retrospective studies, but carefully asserted in a footnote that he had no direct information on the association between smoking and cancer. Incidentally, this footnote contains the curious remark:

"A referee warns me that in spite of the fictitiousness of the figures in Table I and in spite of the emphasis on the methodological character of my remarks, the 'tobacco people' may pick up the argument and use it for publicity purposes."

Also in 1955, Berkson [6] and Mainland and Herrera [7] pointed out certain types of bias which could affect prospective studies.

In 1955, Cutler [8] reviewed the literature. His overall conclusion at that time was "There is disagreement whether the evidence at hand warrants a conclusion that smoking and lung cancer are causally related." He also remarked "If lung cancer should consistently occur more frequently in smokers than in non-smokers, in various subgroups of the populations studied, the cas

* An invited review article on "Smoking and Health," Report of the Advisory Committee to the Surgeon General of the Public Health Service, U. S. Department of Health, Education, and Welfare. Public Health Service Publication No. 1103. Superintendent of Documents, Government Printing Office, Washington, D. C. 20402. xvii, 387 pp. $1.25. Paper.

† I wish to thank J. Berkson, L. A. Goodman, G. W. Haggstrom, and W. H. Kruskal for comments they made on an earlier draft of this review. I also wish to thank several referees for their suggestions.

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for a cause-effect relationship will be greatly strengthened. To refute effectively the hypothesis that smoking is a cause of lung cancer would then require a reasonable explanation, other than causation, for the consistently observed association between smoking and lung cancer."

In 1957, Sir Ronald Fisher [9] offered such an explanation: "that cigarette smoking and lung cancer, though not mutually causative, are both influenced by a common cause, in this case the individual genotype."

Berkson in a series of papers, e.g. [10] and [11], expressed doubt regarding the demonstration of causation. He emphasized that a higher death rate was shown for almost all diseases, and that if this is accepted as reflecting the excess deaths due to smoking then about 40 per cent of all deaths among cigarette smokers must be attributed to their smoking.

In 1959 Cornfield et al [12] concluded that "the consistency of all the epidemiologic and experimental evidence also supports the conclusion of a causal relationship (of lung cancer) with cigarette smoking, while there are serious inconsistencies in reconciling the evidence with other hypotheses which have been advanced."

Of the comments of statisticians, the above seem to be among the more important.

In 1962 the Surgeon General of the Public Health Service of the U. S. Department of Health, Education, and Welfare moved to appoint a committee to "assess available knowledge in this area [smoking vs. health] and make appropriate recommendations" (page 7). It is stated (page 8) that the function of this committee was to make "an objective assessment of the nature and magnitude of the health hazard" and "this committee would produce and submit to the Surgeon General a technical report containing evaluations and conclusions." However, "Recommendations for action were not to be a part" of the committee's responsibility.

The formation of the committee was a formidable operation. The Surgeon General met on July 24, 1962, with representatives of the American Cancer Society, the American College of Chest Physicians, the American Heart Association, the American Medical Association, The Tobacco Institute, Inc., the Food and Drug Administration, the National Tuberculosis Association, the Federal Trade Commission, and the President's Office of Science and Technology. It is noteworthy that no statistical society was represented. Also the list of organisations appears to be heavily weighted towards government agencies and organisations large, general, and active in public relations, and to have low representation of societies with specifically scientific outlooks. The participants of the July 24 meeting compiled a list of 150 scientists and physicians. This list was then screened by these participants, each organisation represented having a power of veto. From the intersection of all the sets of non-vetoes (which might, but apparently did not, have turned out to be the empty set, though we are not told its size) ten were selected for the Committee. Of the ten, only one is listed as a statistician. Since a substantial fraction of the relevant issues are statistical, one might question whether a one in ten representation for statistics was sufficient. However, one further member of the Committee is listed as an epidemiologist.

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The committee met for nine sessions of from two to four days between November 1962 and December 1963, and in addition there were "uncounted" meetings of subcommittees. The committee had the assistance of a professional staff of eight, with a secretarial and technical staff of fifteen. The committee lists 189 individuals or organisations who made "contributions." The literature surveyed was enormous. A basic bibliography of more than 6000 articles from 1200 journals up to 1959 was supplemented by an additional 1100 titles provided by the National Library of Medicine. The Report lists in the references to its various chapters about 900 references. Some of the individual studies considered were themselves enormous. For Hammond's latest report [13], 68,116 volunteers enrolled 1,078,894 men and women.

The Report represents a tremendous sifting, by a large group, of an enormous literature into 387 pages, and this review will confine itself to a brief summary of its contents and an assessment of its major conclusions, with emphasis on statistical and methodological aspects.

The front matter contains no trace of a statement of date of publication. The very last page (page 387) does have as a footnote the notation "U. S. Government Printing Office: 1964 0-714-422" in which I presume the "1964" is the year of publication.

Chapter 1 reviews the evolution of interest in the possible deleterious effects of smoking and the procedures for the establishment of the Committee. Chapter 2 describes the operation of the Committee through its subcommittees, consultants, etc. Chapter 3, "Criteria for Judgment," discusses "the Epidemiologic Method." It remarks (pages 20–21) "Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment . . . To judge or evaluate the causal significance of the association between the attribute or agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment. These criteria include:

(a) The consistency of the association
(b) The strength of the association
(c) The specificity of the association
(d) The temporal relationship of the association
(e) The coherence of the association"

The Report does not define these terms at this point, though they are discussed in pages 182–189 in connection with lung cancer. The Report does not state whether these are jointly sufficient. Nor does this discussion of "the epidemiologic method" give any mention of the factor of self-selection, as discussed by Yerushalmy [14], Yerushalmy and Palmer [15]. Later in the Report (pages 180–181), there is a mention of selection bias, both by the operator of the survey and by the individual whose cooperation is being sought. The subsequent discussion (page 181, last paragraph) is concerned with the results of selection of the type caused by exclusion, or decreased probability of inclusion of persons sick or about to be sick: the discussion does not bear on the well-known fact that volunteers (or equivalently, cooperative persons) may, and often do, differ in their disease experience.

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Chapter 3 also has a section on "Causality," (pages 20–21), the essential part of which appears to be "It is recognized that often the coexistence of several factors is required for the occurrence of a disease, and that one of the factors may play a determinant role, i.e. without it the other factors . . . are impotent . . .

The word *cause* is the one in general usage . . . and is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host."

Presumably in the lung cancer situation *cause* must be defined probabilistically. A very over-simplified sketch might be as follows. Suppose that each individual and his circumstances and environment can be classified dichotomously on each of n classifications, so that he is either an E_1 or an E_1^c, an E_2 or an E_2^c, etc., where E_1^c is the complement of E_1, etc. Suppose now that

$$\Pr\{E_1 | E_2 E_j \cdots E_k\} \neq \Pr\{E_1 | E_2^c E_j \cdots E_k\},$$

where $E_j \cdots E_k$ is some specified subset of conditions $E_3, \cdots, E_n$. Then, for that set of conditions $E_j \cdots E_k$, the probability of E_1 given E_2 is different from the probability of E_1 given E_2^c. Since the presence or absence of E_2 affects the probability of E_1, it seems reasonable to say that E_2 is a *cause* of E_1. The practical significance of E_2 as a cause of E_1 will depend on two conditions:

(a) If the left hand side of the above inequality, though not exactly equal to the right hand side, is numerically quite close, then for that set of $E_j \cdots E_k$ the causative association may be of small practical importance.

(b) If the inequality holds only for, say, one particular subset $E_j, \cdots, E_k$, and for all other subsets equality holds, and if the subset $E_j, \cdots, E_k$ occurs in the population with low probability, then $\Pr\{E_1 | E_2\}$, while not strictly equal to $\Pr\{E_1 | E_2^c\}$, will be numerically close to it, and then E_2 as a cause of E_1 may be of small practical importance. These considerations are related to the Committee's responsibility for assessment of the *magnitude* of the health hazard (page 8). Further complexities arise when we distinguish between cases in which one of the required secondary conditions $E_j, \cdots, E_k$ is, on the one hand, presumably controllable by the individual, e.g. the eating of parsnips, or uncontrollable, e.g. the presence of some genetic property. In the latter case, it further makes a difference whether the genetic property is identifiable or non-identifiable: for example, it could be brown eyes which is the significant subsidiary condition E_j, and we could tell everybody with not-brown eyes it was safe for *them* to smoke.

Chapter 4 is a set of Summaries and Conclusions. Chapter 5 gives consumption of tobacco products, including chewing tobacco and snuff, for the United States for selected years from 1900 to 1962. Chapter 6 is on "Chemical and Physical Characteristics of Tobacco and Tobacco Smoke." Chapter 7, "Pharmacology and Toxicology of Nicotine," concludes that nicotine is unlikely to be important.

In Chapter 8 we come to a discussion of the relationship between smoking and mortality. Subsequent chapters deal with specific groups of diseases: 9, Cancer; 10, Non-Neoplastic Respiratory Diseases; 11, Cardiovascular Diseases; 12, Other Conditions. Chapter 13, "Characterization of the Tobacco

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Habit," concludes that smoking is a *habituation* rather than an *addiction*, "since once established there is little tendency to increase the dose," etc. (page 354). Chapter 14, "Psycho-Social Aspects of Smoking," states that "The overwhelming evidence points to the conclusion that smoking is to a large extent psychologically and socially determined" (page 377). The "psychologically" part of this conclusion is apparently based on Eysenck [16] who found that cigarette smoking was positively associated with extroversion, and that both non-smokers and pipe smokers (the study was made in England, so presumably there were too few cigar smokers to consider) were less extroverted.

The evidence for the "socially" part of the conclusion seems in its summarized form to be not very quantitative. The Report forms the conclusion that "white collar professional, managerial and technical occupations contain fewer smokers than craftsmen, salespersons, and laborers" (page 363), but does not give any figures. However, "As to separate class-linked variables, income does not seem to be related in a consistent manner to prevalence of smoking." The Report finds "The relationship between smoking and education is unclear," and "The proportion of smokers is roughly the same among whites and non-whites." Men smoke more than women, though the discrepancy has been decreasing in recent years. Also, "Smoking (of any kind) is most prevalent among the divorced and widowed and least among those who have never been married, except that among persons over 45, never married are as likely to be smokers as the married" (page 364). Some religions affect smoking, and the rural farm population smoke less than the rural non-farm population. There is little difference between the latter and the urban population. Few figures are quoted in this discussion, so one cannot assess how important these various factors are.

Chapter 15 deals with the morphological constitution of smokers. What seems the most useful information is from Seltzer [17], who in 1942 obtained anthropometric measurements on 922 Harvard undergraduates and in 1950 ascertained their smoking habits (with an 81 per cent response). He found that cigarette only smokers were statistically larger in a number of anthropometric indices than non-smokers, averaging 4.37 pounds heavier, pipe only smokers larger still, and cigar smokers the largest. The Report concludes, however, "The available evidence suggests the existence of some morphological differences between smokers and non-smokers, but is too meagre to permit a conclusion" (page 387). The Report does not give reasons for declining to accept Seltzer's results.

We turn now to a detailed consideration of Chapters 8 and 9.

Chapter 8 reviews the seven major prospective studies and concludes that the overall death rate for cigarette smokers is about 70 per cent higher than for non-smokers. For cigar and pipe smokers the effect was minor. The mortality ratio, i.e. the ratio of the death rate for cigarette smokers to the death rate for non-smokers, was particularly high for certain diseases, e.g. cancer of the lung (10.8), bronchitis and emphysema (6.1), etc. For coronary artery disease the mortality ratio was 1.7. It seems that for effectively all causes of death (even accidents, suicide, and violence) the cigarette smokers had the higher death rate. Though cancer of the lung had the highest mortality ratio "coronary artery disease is the chief contributor to the excess number of deaths

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of cigarette smokers over non-smokers" (page 113). This chapter makes no explicit claim that cigarette smoking is the cause of the mortality ratios being greater than 1.

Chapter 8 reaches its conclusions solely on the basis of seven prospective studies, presumably (though nothing is stated) for the reason that its authors were aware of the hazards in attempting to make rigorous inferences from retrospective studies (possible biases in retrospective studies are discussed in Chapter 9, pages 180–181). The main difficulty, it seems to me, is that it is very difficult to define accurately the population from which the hospital sample of, e.g., cancer patients has been drawn, and even more difficult to draw a sample of controls from that population.

In some of the prospective studies a clearly defined population existed, e.g., policy holders of U. S. Government Life Insurance Policies, and the intention was to take a 100 per cent sample of this population, but in general for these studies non-response averaged 32 per cent. Biases in the non-respondents could play havoc with inferences based on the respondents. Appendix I to Chapter 8 considers this, and on various assumptions about the behavior of the non-respondents concludes that such biases could, under rather extreme assumptions, make an actual mortality ratio of, for example, 4.0 be observed as 5.0, or an actual 7.0 be observed as 10.0. The possible effects of the non-respondents are tricky, however, as Doll found (page 97) that for British doctors the non-respondents had a higher death rate and relatively more smokers than the respondents. The cross-classification is, however, not given.

In other prospective studies, e.g. the 1963 Hammond study, there is no clearly defined population and hence the concept of percentage response is impossible to evaluate. Bias could exist in the recruitment into the sample, but it is stated (page 181) that its effects, if any, should decrease with time, and this is not observed. Mainland and Herrera [7] had previously wondered about the effects of biases in studies of this type, but the Report cites the gradual increase in the mortality ratio with time as weakening their criticism. The 1963 Hammond study specifically excluded "persons too ill to answer a questionnaire" (also illiterates, and persons who could not have been traced). Presumably these exclusions are responsible for the age adjusted death rate of the Hammond sample being substantially below that of U. S. males generally. In fact, for all seven prospective studies the samples are healthier than U. S. males (page 95). This may be largely due to the probable fact that the surveys are drawn from relatively high socio-economic groups. In specific surveys other reasons may also operate.

Even though cancer contributes only 26 per cent to the total excess number of deaths of cigarette smokers, it receives the most attention in the Report, as Chapter 9 being 136 pages is substantially the largest. Lung cancer, which contributes 16 per cent to the total number of excess deaths, receives the greatest emphasis and we will confine our attention accordingly.

Chapter 9 first reviews age-adjusted mortality rates for various countries, for various times (1900–1960), by site, by sex, income class, occupation, and ethnic group. It then discusses various carcinogens, some of which are present in tobacco smoke. Then follows pages 149–196 on lung cancer, reaching the

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conclusion (page 199) "Cigarette smoking is causally related to lung cancer in men." We will now summarize the arguments that led to that conclusion.

Pages 150–161 review 29 retrospective studies and, briefly, the 7 prospective studies that had been discussed in Chapter 8. There follows a discussion of attempts to induce lung cancer with tobacco extracts and tobacco smoke in experimental animals. These have not been successful. However, industrial carcinogens were effective. Another section (page 167) reports that "genetic factors exert a determining influence on the spontaneous development and induction of lung tumors in mice."

Pages 175–176 discuss the correlation of national crude male death rates for lung cancer with per capita consumption of cigarettes. Using a 20 year lag, Doll obtained $r = 0.73$ with 11 countries. The "population" from which these 11 countries were "sampled" is not described.

Pages 179–182 discuss possible biases being responsible for the observed association, and concludes that the observed association is real.

The Report then moves to establish the causal significance of the association, its arguments following the five criteria that Chapter 3 listed as being part (or all?) of the "epidemiologic method."

(a) The first criterion is "consistency." The 29 retrospective and the 7 prospective studies all demonstrate the same association.

(b) "The most direct measure of the strength of the association between smoking and lung cancer is the ratio of lung cancer rates for smokers to non-smokers . . . " It is high, of the order of 9 to 1. Also "Important to the strength as well as to the coherence of the association is the dose-effect phenomenon. In every prospective study that provided this information, the dose-effect was apparent . . . "

(c) The specificity of the association "implies the precision with which one component of an associated pair can be utilized to predict the occurrence of the other." This seems a curious use of the word "specificity." A more satisfactory definition would seem to be Yerushalmy and Palmer's [15] "The basic assumption of such a test for specificity is that if the characteristic is not related to the disease in a causal way, then the relationship should not be restricted to the disease under study but should also be present with other disease entities. If the characteristic can be shown to be related only or mostly to the disease under study and not to many other disease entities, then our confidence that it is a cause-carrying vector for that disease is greatly increased."

This section of the Report discusses both these interpretations, its own and Yerushalmy and Palmer's, of "specificity." On the first, it comments that with diseases with multiple causes one cannot expect high specificity in this sense.

On the second, the Report states "The number of diseases in which the ratios remain significantly high, after consideration of the non-response bias, is not great enough to cast serious doubt on the causal hypothesis."

It further comments that even a single substance might cause several diseases and a mixture of substances, such as occur in tobacco smoke, might "produce more than a single disease." The Report concludes "Thus, it is reasonable to conclude that the association between cigarette smoking and lung cancer has a high degree of specificity."

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(d) The next section, "Temporal Relationship of Associated Variables," makes the point that people smoke and then have cancer, rather than vice versa. The point of course, is that if *B* occurs later in time than *A* then it is difficult to maintain that *B* is a cause of *A*. This is obviously a necessary condition, but not sufficient.

(e) The final criterion is the "Coherence of the Association" which covers a number of points as follows.

(1) The historical increase in cigarette consumption is correlated with the historical increase in lung cancer.

(2) The sex difference in smoking is in the same direction as the difference in lung cancer rates.

(3) Page 186 reports that "although adjustment for smoking history does not equalize the urban-rural lung cancer mortality ratio, control on the urban-rural residence factor nevertheless leaves a large mortality risk difference between smokers and non-smokers." This seems to imply that correlation of residence with smoking cannot account for the observed association of lung cancer rate with smoking, and, vice versa, correlation of smoking with residence cannot account for the observed association of lung cancer with residence.

(4) A section on socio-economic differentials in lung cancer mortality remarks (page 187) "it will be nevertheless noted that the professional and farmer and farm manager groups had higher proportions of non-smokers among them than did the laborers and craftsmen. This finding is in the proper direction for compatability with the socio-economic differential in lung cancer mortality but the disparity does not appear to be sufficient to provide a satisfying correction."

(5) This section comments on the dose-response relationship and refers to the muddled position with respect to inhalation.

A section on the histopathologic evidence (page 189) refers mainly to work by Auerbach on epithelial changes in the trachea and bronchi:

"These changes were rarely seen among non-smokers, but increased in frequency and intensity with the number of cigarettes smoked daily by individuals without cancer and were most frequent and intense in patients dying of lung cancer." The opinion is expressed (page 172) "it seems probably that some of the lesions found in the tracheobronchial tree in cigarette smokers are capable of developing into lung cancer."

It is difficult for one not a specialist in this area to assess the significance of these observations. The Report concludes (page 189) "Thus, the histopathologic evidence derived from laboratory and clinical material support the cigarette smoking—lung cancer hypothesis" so the Committee does not appear to regard this time as crucial. Presumably having established to its satisfaction that smoking causes lung cancer since the criteria of the "epidemiologic method" are allegedly satisfied, the Report in pages 190–193 discusses the "Constitutional Hypothesis," i.e. "the alternative hypothesis that both smoking of cigarettes and cancer of the lung have a common cause . . ." and concludes "that genetic factors play a minor role" (page 192). The main

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reasons for this conclusion appear to be (a) the presumption that the genetic hypothesis would have to be very complicated to include the dose-response relationship, etc., and (b) the rapid historical rise of lung cancer.

Finally, sundry factors such as occupational hazards, urbanization, air pollution, etc., are mentioned, and on page 196 the conclusion of causality is unequivocally stated.

This review has so far been largely restricted to a summarization of the relevant arguments leading to the above important conclusion. I will now discuss the question of whether the available evidence justifies the Report in reaching that conclusion. It is possible, of course, for the conclusion to be in fact correct but for the evidence in its favor to be inadequate. We are all familiar with the accused who has to be found not guilty, because of insufficient evidence, though we are personally certain of his guilt. Let us now comment on various parts of the Report's position.

In my opinion a key factor in determining one's opinions is one's interpretation of Table 26, pages 109–110, which shows the mortality ratios, individually by separate study and also jointly, for 25 causes of death, ordered from cancer of lung with a total mortality ratio of 10.8, bronchitis and emphysema with a total mortality ratio of 6.1, down to cancer of the rectum (1.0) and cancer of the intestines (0.9). The latter cause of death is the only one out of the 25 to show a total mortality ratio of less than 1. The total over all studies column of Table 26 is reproduced here as Table 1. The median of the 25 total mortality ratios is 1.5, and 8 are greater than 2.0. One could adopt an extreme null hypothesis attitude and admit that only those causes of death for which the total mortality ratio was statistically significantly greater than 1 are genuinely associated with cigarette smoking. The technical details of this statistical problem would be difficult on account of the various "sampling" procedures involved, allowances for possible biases and dependencies, the varying sample sizes, and the multiplicity of the tests being made. If we take the twenty-first cause of death, "accidents, suicides, and violence," with a total mortality ratio of 1.2, it is noteworthy that in each of the seven separate studies the mortality ratio is greater than 1. In my opinion virtually every tabulated cause of death shows a mortality ratio greater than 1. I do not regard even the twenty-fifth cause of death, cancer of the intestines, as significantly an exception to this, as if we look at estimates of 25 parameters the smallest of the 25 is likely to be smaller than its population value, and at 0.9 it would not take much of a sampling error to bring the ratio over 1. However, whether one feels that probably all 25 causes of death have mortality ratios greater than 1, or merely the first 21 out of the 25, or the first 15, makes little difference in my opinion. In the discussion I give below, I shall use the phrase "virtually all causes of death" but it could be replaced by some such phrase as "21 out of 25 causes of death" without changing appreciably the import of the discussion.

One's interpretation of Table 26 determines whether one accepts the Report's conclusion (page 185) "Thus, it is reasonable to conclude that the association between cigarette smoking and lung cancer has a high degree of specificity" as, on the one hand, reasonable, or on the other hand, as an extraordinary statement completely in violation with the facts. The Report

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TABLE I. NUMBERS OF EXPECTED AND OBSERVED DEATH FOR SMOKERS OF CIGARETTES ONLY, AND MORTALITY RATIOS, TOTALLED OVER ALL SEVEN PROSPECTIVE STUDIES. TAKEN FROM TABLE 26, PAGE 110, OF THE REPORT

Cause of death	Deaths		Mortality ratio
	Expected	Observed	
Cancer of lung	170.3	1,833	10.8
Bronchitis, emphysema	89.5	546	6.1
Cancer of larynx	14.0	75	5.4
Cancer of oral cavity	37.0	152	4.1
Cancer of esophagus	33.7	113	3.4
Stomach and duodenal ulcers	105.1	294	2.8
Other circulatory diseases	254.0	649	2.6
Cirrhosis of liver	169.2	379	2.2
Cancer of bladder	111.6	216	1.9
Coronary artery disease	6,430.7	11,177	1.7
Other heart diseases	526.0	868	1.7
Hypertensive heart disease	409.2	631	1.5
General arteriosclerosis	210.7	310	1.5
Cancer of kidney	79.0	120	1.5
All other cancer	1,061.4	1,524	1.4
Cancer of stomach	285.2	413	1.4
Influenza, pneumonia	303.2	415	1.4
All other causes	1,508.7	1,946	1.3
Cerebral vascular lesions	1,461.8	1,844	1.3
Cancer of prostate	253.0	318	1.3
Accidents, suicides, violence	1,063.2	1,310	1.2
Nephritis	156.4	173	1.1
Rheumatic heart disease	290.6	309	1.1
Cancer of rectum	207.8	213	1.0
Cancer of intestines	422.6	395	.9
All causes	15,653.9	26,223	1.68

accepts "specificity" as one of the criteria of "the epidemiologic method" (pages 20, 183), and in my opinion the way it claims the facts are in conformity with the criterion is to flatly ignore the facts.

In my opinion, therefore, Table 26 raises difficulties which the Report totally fails to face up to. The difficulties are as follows.

If one believes that the observed association between smoking and lung cancer is substantially real, and not an artefact of biased sampling, then one would seem required also to accept the observed association between smoking and almost all causes of death as substantially real.

If one believes that the observed association between cigarette smoking and virtually all causes of death is substantially real, then one must take one of the following positions:

(a) All the associations are due to causation.

(b) Some of the associations are due to causation and others to correlations, concealed or otherwise.

(c) All of the associations are due to correlations, concealed or otherwise.

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Positions (a) and (c) may present the fewest difficulties. If one adopts position (a), then one is under some obligation to provide hypotheses as to possible mechanisms, or to hold out hope that future research will provide these hypotheses. The difficulty with the smoking hypothesis is that it has not really got to first base on even lung cancer, let alone the other 24 causes of death, even though the matter has been under intensive investigation for ten years or more.

The most potent carcinogen identified in tobacco smoke is benz (a) pyrene (page 27) and "it is present in much larger quantity than any of the other carcinogens listed." Cigar smoke has almost 4 times as much benz (a) pyreme, and pipe smoke about 10 times as much as cigarette smoke (page 58), yet pipes and cigars are pretty well innocent of the charge of association with lung cancer. (However, the Committee does conclude that the smoking of pipes is causally related to cancer of the lip (page 204).)

Apart from the above specific measurements on smoke, the difference between cigarettes and cigars (and pipes) is a puzzling feature of the indictment of tobacco. It could be, of course, that the variety of tobacco used differs significantly, that the tobaccos are cured differently, that cigars and pipes do not use cigarette paper, that possibly pipes and cigars burn at lower temperatures, or that many cigarette smokers inhale whereas few pipe or cigar smokers do. But if inhalation is the crucial item, then it should show up strongly when cigarette smokers are analyzed into inhalers and non-inhalers, and as reported above, the present evidence on this point is not clear.

As stated earlier, animal experiments to demonstrate carcinogenic effects of tobacco smoke have proved unsuccessful.

While hypotheses for a causative effect for lung cancer are still unsatisfactory after a decade of research, the situation is even emptier for other diseases.

The degree of one's belief in the plausibility of the smoking hypothesis thus is considerably affected by the extent to which one thinks it probably that satisfactory mechanisms will be provided to account for all, or most, of the diseases.

If one adopts position (b), then one is in the unenviable position of admitting that concealed correlations account for diseases D_i, $i=k, k+1, \cdots, n$, but are not responsible for diseases D_i, $i=1, 2, \cdots, k-1$. It seems to me that once one admits that concealed correlations account for a substantial number of the observed associations, then one has to work very hard to disprove the hypothesis that they may account for all the observed correlations.

The Report uses the historical correlation of rise in lung cancer mortality with increase in per capita consumption of cigarettes as one factor to support the coherence of the association (page 185). All statisticians know that the presence of a positive, zero, or negative correlation between two variables observed over time has been the basis of more ludicrous nonsense than any other statistical procedure. For example, the incidence of cancer of the stomach has been declining for many years (Dorn and Cutler [18]), but only a madman would infer that the increased smoking has caused the decreased stomach cancer. Incidentally, it is surprising that the Report makes no mention of this fact in the section on stomach cancer (pages 225–229) though it is mentioned

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on page 135. The Report omits any comment on the weakness of this item in its discussion of the "Coherence of the Association" on page 185.

Similar considerations apply to spatial correlations, which are presented on page 176.

The fact that the hypothesis that cigarette smoking is a cause of cancer appears by and large to be in conformity with the data, and hence that this hypothesis is acceptable, does not rule out the possibility that there are other hypotheses also in conformity with the data. As Sir Ronald Fisher [19] wrote almost thirty years ago:

"For the logical fallacy of believing that a hypothesis has been proved to be true, merely because it is not contradicted by the available facts, has no more right to insinuate itself in statistical than in other kinds of scientific reasoning." And as Yule [20], quoted by Irwin [21], wrote about forty years ago: " 'You can prove anything by statistics' is a common gibe. Its contrary is more nearly true—you can never prove anything by statistics. The statistician is dealing with the most complex cases of multiple causation. He may show that the facts are in accordance with this hypothesis or that. But it is quite another thing to show that all other possible hypotheses are excluded, and that the facts do not admit of any other interpretation than the particular one he may have in mind."

It is not clear to me what are the optimal, or even satisfactory, procedures for inference. In the case where there are two competing hypotheses, one might estimate the "plausibility ratio," analogous to the likelihood ratio, and if it is very small, $\ll 1$, or very large, $\gg 1$, one can reach a conclusion. If the plausibility ratio is in the neighborhood of 1, then no decision can be reached. One would further wish that if the more plausible hypothesis is chosen as a null hypothesis, then a test of this null hypothesis can be accepted at a large P value, for otherwise one would suspect that neither hypothesis was correct, and if the less plausible hypothesis is tested as a null hypothesis one would want to it be rejected at a small P value.

The main alternative to the smoking causes-cancer hypothesis is the genetic hypothesis, and there are several odd pieces of information that give plausibility to it.

(1) There is some evidence that non-smokers, cigarette smokers, and pipe and cigar smokers are morphologically different (Chapter 15, reference to Seltzer [17]).

(2) There is some evidence that the various classes of smokers and non-smokers are psychologically different (Chapter 14, reference to Eysenck [16]).

(3) There is some evidence that identical twins are more alike than non-identical twins in their smoking habits (page 190, references to Fisher [22], Friberg et al [13], and Raaschou-Nielsen [24]).

(4) "Foreign-born migrants to the United States as a group have age-adjusted death rates for cancer of the esophagus and stomach about twice those recorded for native-born white males and females," etc., (page 134).

(5) "The several ethnic groups in the United States display their own characteristic patterns of successes and deficits in risk by site" of cancer (page 135).

It is true, of course, that these phenomena ((4) and (5)) could be the result

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of social, dietary, or other customs imported by the immigrants and maintained for one or more generations, or could be a confounding of the effects of the environment of the region of the U. S. in which each ethnic group tended to settle. Thus these phenomena can be interpreted in terms of environmental effects rather than genetic effects.

(6) Yerushalmy [14] presented data strongly suggesting that whether or not the husband smokes is associated with the incidence of premature births.

(7) Hammond [13] gives results showing marked association of death rate with longevity of parents and grandparents.

On my reading, the main reasons the Report gives for rejecting the genetic hypothesis are (1) the necessary complexity of the genetic hypothesis, and (2) the unlikelihood that the genetic pool can have changed sufficiently in the past fifty years to account for the historical rise in lung cancer rate.

For the first difficulty, different genotypes need to be hypothesized for the various classes such as cigarette smokers, cigarette smokers who give up cigarette smoking, cigar smokers, etc. It seems to me that an enormous number of traits are transmitted genetically, from color of skin and tendency to diabetes and tendency to baldness, and it is completely plausible that the tendency to be a cigarette smoker in varying degrees, a pipe or cigar smoker, and so on can be carried by the genetic code.

The second objection referred to above seems to me to overlook a possible fallacy in the interpretation of historical change in death rates. Firstly, possibly part of the long term apparent rise may be an illusion caused by fashions in diagnosis and by improvements in diagnostic techniques. It is quite probable that several decades ago many cases of lung cancer would have been diagnosed as tuberculosis. The Report claims (page 140) that over the shorter term, from 1947 on, particularly for data for Connecticut and New York, the increase in genuine as there have been "no significant advances in diagnostic methods" and in these regions "a high percentage of the cases reported have microscopic confirmation." This comment does not quite bear on the point at issue. The suggestion of the skeptics is not that cases of tuberculosis are now being falsely diagnosed as lung cancer but on the contrary that in the past cases of lung cancer were falsely diagnosed as tuberculosis.

The second argument is more complex. The generation born in 1880 reached the age of 20 in 1900, and a substantial fraction, 24 per cent, had died by this time, presumably largely due to the traditional infectious diseases of childhood. The generation born in 1900 reached the age of 20 in 1920, and a lesser fraction of this generation had died by that age, namely 15 per cent. Therefore, the 1900 cohort at the age of 50 represents quite a different stratum from the 1880 cohort at the same age of 50, since the former includes the "weaklings" who were eliminated from the latter. The relatively large number of cases of lung cancer observed in the 1900 cohort can merely be largely those who would not have survived to run the risk of lung cancer if they had been born 20 years earlier. On this model the alleged historical increase in rate of lung cancer can be readily accounted for. The model is speculative, however.

Rather strangely, the Report does not include in the section devoted to refuting the constitutional hypothesis (pages 190–193) the observations by Corn-

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TABLE 2

	X		X^c		Sums over X and X^c	
	S	S^c	S	S^c	S	S^c
C	0.00450	0.00050	0.00005	0.00045	0.00455	0.00095
C^c	0.44550	0.04950	0.04995	0.44955	0.49545	0.49905
Sums	0.45000	0.05000	0.05000	0.45000		

field et al [12] that if the mortality ratio for smokers to non-smokers for a particular disease is k, then factor X must be present at least k times more frequently among smokers than among non-smokers. The Report does refer to this result, without citation of source, in the section on specificity (page 184), where its relevance escapes me. It is clear, however, that Cornfield et al regard this result as one of the key arguments against the constitutional hypothesis, as they cite it prominently in the Summary to their paper [12]:

"The magnitude of the excess lung cancer risk among cigarette smokers is so great that the results can not be interpreted as arising from an indirect association of cigarette smoking with some other agent or characteristic, since this hypothetical agent would have to be at least as strongly associated with lung cancer as cigarette use; no such agent has been found or suggested."

A simple arithmetical illustration of this (mathematical) phenomenon is developed below. Suppose that the population is divided 50:50 into X and X^c. Suppose that amongst X people the probability of being a smoker is 0.9 and the probability of getting cancer is 0.01, and that these probabilities are independent. Suppose further that among X^c people the probability of being a smoker is 0.1 and the probability of getting cancer is 0.001, and that these probabilities are independent. Then the resulting probabilities are in Table 2. The cancer rate among smokers is $0.00455/(0.00455+0.49545)=0.0091$ and the cancer rate among non-smokers is $0.00095/(0.00095+0.49905)=0.0019$: the mortality ratio for cancer for smokers/non-smokers is thus $0.0091/0.0019=4.79$. The X rate among smokers is $0.45/(0.45+0.05)=0.90$ and among non-smokers is $0.05/(0.05+0.45)=0.10$; the ratio for X for smokers/non-smokers is thus $0.90/0.10=9.0$. This illustrates Cornfield et al's point that the X ratio for smokers/non-smokers must be greater than the mortality ratio for smokers/non-smokers. I do not feel that the numerical values of the parameters inserted in this simple model are ridiculous, yet with independence of S and C for X and for X^c we came out with a large mortality ratio for the population as a whole. I do not see why the fact that the X ratio is larger than the mortality ratio is any embarrassment to the constitutional hypothesis.

The Report quotes various results from Hammond's latest report [13] which illustrates various phenomena which can be attributed to various constitutional hypotheses, though one could also easily construct other causal hypotheses in each case. The "effect" of the use of tranquilizers, for example is shown in Table 3. (All numbers quoted in Tables 3–6 are age standardized death rates from all causes for males.) Recalling that this data was collected by volunteers,

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TABLE 3

Tranquilizers	Never smoked regularly	Cigarettes 20+ a day
Do not use	755	1501
Use	1308	2286

TABLE 4

Fried Food	Never smoked regularly	Cigarettes 20+ a day
No Fried Food Eaten	1208	2573
Fried Food 3-4 times a wk.	642	1714

often in a "social" environment, it is probable that some tranquilizer users did not admit to this habit, and therefore appear in the "do not use" row, hence raising the death rate for this row. The real "effect" of tranquilizers is therefore probably even more dramatic than the table shows.

Tables 4, 5, 6 are from Hammond; the first two are not quoted in the Report. Hammond's data also show the well known, but as far as I know, never satisfactorily explained, differences in death rates between married, single, widowed, and divorced persons. It also shows a marked hereditary effect, a marked height effect, and a moderate education effect. Hammond does not give cross-classifications, other than on smoking.

It is noteworthy that in all the above two-way cross-classifications, and others in Hammond's report not quoted here, the smoking category always has

TABLE 5

Sleep	Never smoked regularly	Cigarettes 20+ a day
<5 hrs.	2029	3936
5 hrs.	1121	2655
6 hrs.	805	1601
7 hrs.	626	1426
8 hrs.	813	1562
9 hrs.	967	1729
10+hrs.	1898	2694

TABLE 6

Exercise	Never smoked regularly	Cigarettes 20+ a day
None	834	1416
Slight	579	1347
Moderate	486	1065
Heavy	474	998

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the higher death rate. The Report mentions an unpublished analysis supplied to the Committee by Ipsen and Pfaelzer, with the conclusion, "Further, the correlation of any of these variables with cigarette smoking was too weak to reduce markedly the correlation of cigarette smoking with mortality after adjustment for the other variable." It is a pity that the Report does not give any detail on this analysis, as it may be that this analysis would have carried the greatest conviction. However, this is speculation, and we can only judge the Report by what it contains and by its references to the published literature.

One can interpret the results of Tables 3–6 in various ways. The association with longevity of parents and grandparents probably has a genetic interpretation, though it is possible to interpret it environmentally: it could be that the grandparents settled in an environment or adopted habits and customs that were favorable to longevity, and which they passed on to the later generations. The association with tranquilizers could be interpreted as causal, as is the association with cigarettes, but it appears equally plausible to hypothesize that the need for tranquilizers, and/or cigarettes, is merely a reflection of an underlying facet of the human organisms involved. Likewise, the associations with fried food eating, sleep, and exercise can be interpreted either as causal or as concealed correlations.

It will be recalled that the Committee's assignment was "if possible, to reach some definitive conclusions on the relationship between smoking and health in general" (page v).

"This committee would produce and submit to the Surgeon General a technical report containing evaluations and conclusions" (page 8).

The Committee's "Judgment in Brief" was "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action" (page 33).

The detailed conclusions cover pages 37–40; the most important are "Cigarette smoking is causally related to lung cancer in men."

"Male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance."

My opinion is that the Committee has not established the case for causality in lung cancer. My reasons for this opinion are, to recapitulate;

(a) This conclusion can only be justified by proving the genetic hypothesis to be false, and this the Committee has failed to do.

(b) Even if there was no competing hypothesis, the case for causality is at the present time significantly weakened by the gross nonspecificity of the association and by the absence of hypothetical physical-chemical mechanisms.

My opinion that the Committee has failed to offer a satisfactory proof of the hypothesis of causality does not imply that I believe that the causality hypothesis has been proved false. It implies nothing more than I believe that it is not possible to reach definitive conclusions at this time.

Although "Recommendations for actions were not to be part of the Phase I committee's responsibility" (page 8), yet as noted above the Committee did conclude that "appropriate remedial action" was warranted. I take this as an excuse to append some personal reflections.

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Passing over the question of whether any governmental action is warranted, each individual cigarette smoker has to decide whether to make the effort to give up cigarette smoking. To make this decision he would need to know (a) the change in his expectation of life assuming that lung cancer alone is causally connected with cigarette smoking, (b) the change in his expectation of life assuming that virtually all causes of death are causally connected with cagarette smoking.

The Report does not appear to provide these figures (searching in the Report for any particular topic is sometimes difficult as the Report has no index), which is rather surprising in view of the fact that an assessment of the *magnitude* of the health hazard was one of the Committee's prime responsibilities (page 8).

The individual cigarette smoker would then have to weight the above changes in expectation by his assessment of the question of whether the cigarette smoking was a cause. He would have to relate this expected change in expectation of life to the analogous probable expected changes in expectation of life caused by various other of his activities which probably cause decreases in expectation of life, such as over-eating, undersleeping, under-exercising, travelling by automobile, etc. He would also have to weigh the possibility of such adverse consequences of giving up smoking as in due course becoming appreciably overweight. He would have to assign utilities to the expected change in expectation of life and to the pleasure and satisfaction he gets from cigarette smoking.

It is unfortunate that the Report does not give a table of changes in expectation of life, for if the change at, say, age 30 was 10 years, then even if one assigned a probability of 1/5 to the cigarette smoking causality hypothesis being true, the net change of 2 years would give one pause to consider, whereas if the change at age 30 is only 2 years, then the net change of 0.4 years on an average expectation of about 40 years might not be taken too seriously by some people.

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In summary, a significant association has been established between cigarette smoking and the incidence of myocardial infarction and sudden death in males, especially in middle life, in population groups whose members appear so far to be similar except for smoking habits. The question of whether they are, in fact, similar except for smoking is, of course, basic to the problem of whether cigarette smoking actually promotes the development of coronary disease or whether it is closely associated with some other factor or factors which promote the development of coronary disease. It has been pointed out that angina pectoris, which indicates advanced coronary atherosclerosis, is less closely associated with cigarette smoking than is myocardial infarction, and that this suggests that any etiologic role of smoking in myocardial infarction should relate more to acute occlusive mechanisms, such as intravascular thrombosis or coronary spasm, than to the development of chronic arterial disease.

SMOKING AND NON-CORONARY CARDIOVASCULAR DISEASE

In surveys of large groups cigarette smoking has not been found to be associated with an increased prevalence of hypertension (3, 4, 19, 47, 49). The study of Hammond and Horn (40, 42) did not show an increased death rate from hypertension in smokers. However, Dorn (22) found that the death rate of cigarette smokers from hypertension with heart disease was 1.53 times that of non-smokers, and from hypertension without heart disease, 1.41 times that of non-smokers. Hammond's current study shows similar figures (41). Smoking has not been found to be associated with an increased mortality rate from chronic rheumatic heart disease (22, 41, 42).

Hammond and Horn (42) found a moderate increase in the mortality rate from cerebral vascular disease in cigarette smokers as compared to non-smokers (ratio 1.30). Dorn (22) reported a ratio of 1.33, and Hammond (41) a ratio of 1.43. Although non-syphilitic aortic aneurysm is a relatively infrequent cause of death, the mortality ratio for smokers to non-smokers in this diagnostic category is large in relation to the ratios in other cardiovascular disorders. In the study of Hammond and Horn (42) it was 2.72, and in Hammond's current study (41) it is 3.10.

It has been reported (100) that diabetic males who smoke have a 50% greater incidence of clinically detectable arteriosclerosis obliterans in the legs than those who do not smoke. In general, however, there is little information about the relation of smoking to peripheral arteriosclerosis. Most experienced clinicians advise patients with obliterative peripheral arterial disease to stop smoking (45).

Buerger's disease, or thromboangiitis obliterans, has been traditionally associated with smoking, and the literature contains numerous clinical reports describing the arrest of Buerger's disease when smoking is stopped and its reactivation on resumption of smoking. The existence of Buerger's disease as an entity separate from arteriosclerosis obliterans has been recently challenged (101), but well defended (61).

It is apparent that much more work will have to be done to determine what relationship may exist between non-coronary occlusive vascular disease, aneurysmal disease, and smoking.

CHARACTERISTICS OF CIGARETTE SMOKERS

If it could be shown that cigarette smokers and non-smokers had significant constitutional differences apart from any differences that might be caused by smoking itself, then a possibility would exist that some predisposition of smokers to a particular disease might also be of constitutional origin and not caused by smoking. Cigarette smokers have, in fact, been found to differ as a group from non-smokers, but the differences, such as serum cholesterol concentration and resting heart rate, could have resulted from the smoking habit itself, so far as present knowledge indicates.

The concentration of serum cholesterol has been found to be slightly higher in smokers than in non-smokers by a number of investigators (6, 13, 49, 63, 95), but others have found no relationship (1, 54). Dawber (19) found not only that serum cholesterol was higher in smokers than in non-smokers but also that it remained higher in those who stopped smoking.

Smokers tend to be leaner than non-smokers, but to gain when they stop smoking (3, 18, 49).

A few personality differences have been reported between cigarette smokers and non-smokers. Friedman's type A men (the coronary type) tended to be heavy smokers (33). Smokers are said to be more easily angered and to eat more when under stress (94). They have been reported to marry oftener, to change jobs more frequently, to be more often hospitalized, and to participate more actively in sports than non-smokers (60).

Thomas (91, 95) has reported that the parents of medical students who smoke have a significantly higher incidence of arteriosclerotic and hypertensive cardiovascular disease than parents of non-smokers. Clearly, this finding is open to more than one interpretation.

Smokers tend to have a higher heart rate than non-smokers (3, 94).

The matter of constitutional predisposition to smoking has been investigated in twins. It has been found (27, 28, 32) that the smoking habits of monozygotic twins are significantly more alike than those of dizygotic twins, even when members of a twin pair are brought up separately.

In spite of some bits of suggestive evidence the existence of basic constitutional differences between smokers and non-smokers is not presently established. The constitutional hypothesis, which links smoking and predisposition to disease, is discussed in detail in Chapter 9, Cancer.

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The two reports that did not describe a relationship between cigarette smoking and serum cholesterol levels are (1) Acheson and Jessop (in old men) and (54) Konttinen in young men. These are well executed studies and are reproduced in this report. This subject is discussed on pages 207 to 210. Subsequent to 1964, ten additional reports appeared indicating no relationship between cigarette smoking and hyperlipidemia..

TOBACCO SMOKING AND SERUM LIPIDS IN OLD MEN

BY

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The interrelationships between coronary heart disease, serum lipids, and cigarette-smoking have been demonstrated by authors from several countries in recent years (Hammond and Horn, 1954; Gertler and White, 1954; Gofman *et al.*, 1955; Doll and Hill, 1956; Thomas, 1958; Karvonen *et al.*, 1959; Dawber *et al.*, 1959; Bronte-Stewart, 1961). Their work has, however, been chiefly concerned with men below or during middle age, whereas it seems that over the age of 65 years there is little relationship between death from coronary heart disease and a previous history of smoking (Doll and Hill, 1956) or between clinical evidence of myocardial ischaemia and raised serum cholesterol (Oliver, 1958; Acheson, 1961). It is therefore a matter of some interest whether serum lipids are related to smoking habits in men aged 65 and over.

Material and Method

The Sample.—The men were all pensioners on the list of Messrs. Arthur Guinness Son and Company Ltd (Dublin), and their names were selected in a random manner as follows: every man aged between 75 and 8[illegible] was chosen, between the ages of 70 and 74 every third name was omitted from the list, and between the ages of 65 and 69 alternate names were omitted. The method of selection produced 267 names in all, and each man was sent a postcard inviting him to attend in the company's medical department for clinical examination; the actual attendances (221) are shown by age in Table I, together with the numbers for whom estimations of serum cholesterol and an analysis of the serum proteins by paper electrophoresis were satisfactory.

TABLE I.—*The Sample*

Age in Years	Number of Men						
	Invited to Attend	Attended		With Complete Cholesterol Assessments		With Complete Serum Electrophoresis	
		No.	%	No.	%	No.	%
65–69	92	82	89	74	80	72	78
70–74	100	86	86	83	83	77	77
75–79	40	29	72	29	72	29	72
80–85	35	24	69	23	66	23	66
Total	267	221	82	209	78	201	75

Clinical Examination and Lipid Estimations.—Full details have already been published of clinical procedures (Acheson and Acheson, 1958; Acheson, 1961) and of biochemical and electrophoretic techniques (Acheson *et al.*, 1958; Acheson and Jessop, 1961); accordingly only an outline will be given here. The clinical examination, which was carried out by one of us (R. M. A.), included a history of smoking habits and a note about diet that permitted a rough appraisal of whether or not these old men fed themselves adequately. Blood was taken in a dry syringe between 9 a.m. and 11 a.m., after breakfast, and within 90 minutes the serum was separated by centrifuging. The serum cholesterol was estimated by three independent observers, one of whom used the method of Sackett (1925) and two that of Anderson and Keys (1956); and since the findings by the two methods did not differ systematically the results were averaged, when the three estimations were within 10% of the highest of the three. In the relatively few cases where they were not, assessments were repeated until the required agreement level was reached. Paper electrophoresis, with certain minor modifications, was carried out by the technique of Dangerfield and Smith (1955), using a horizontal EEL apparatus and a barbitone buffer (*p*H 8.6). Each strip was divided in two, light green S.F. ("lissamine" green) being used to stain the serum proteins and sudan black for the lipoproteins. The intensity of staining in the various bands was measured with an automatic reflectance scanner which incorporated its own integrator.

Tobacco and Dietary Indices.—For certain of the calculations tobacco and dietary indices have been used. For the tobacco index 1 oz. (28 g.) of tobacco a week and 5 cigarettes a day were taken as unity. Thus a man who smoked 20 cigarettes a day had an index value of 4, and another who smoked 10 cigarettes a day and 3 oz. (85 g.) of pipe tobacco a week had a value of 2+3=5. The dietary index simply enumerated the number of times a man ate meat, fish, or egg in a week; it ranged from 0 to 19, and, although it is obviously a very rough measure, the serum albumin was significantly higher in those with an index of 14 than in those with an index of less than 2; and men with an index of 2 or under had significantly less subcutaneous adipose tissue than the remainder of the sample (Acheson and Jessop, 1961).

Results

Relationship of Serum Cholesterol and Smoking With Age

The distribution of serum cholesterol in the sample is shown by five-year age-groups in Fig. 1 and that of β/α lipoprotein ratio in Fig. 2. There tended

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to be absolutely and relatively fewer men with a serum cholesterol in excess of 220 mg. among the older age-groups, with the result that the mean value fell slightly

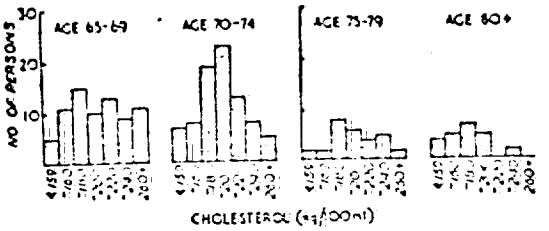

FIG. 1.—Histograms showing distribution of serum cholesterol in sample by five-year age-groups.

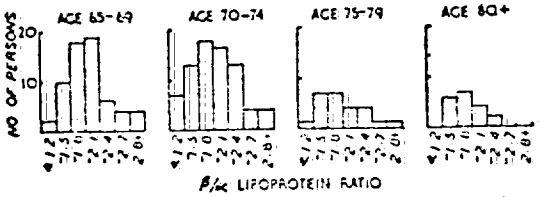

FIG. 2.—Distribution of β/α lipoprotein ratio by five-year age-groups.

but significantly with age ($r = -0.19$; $P<0.01$). The pattern of smoking varied in a far more striking manner with age (see Table II); 66% of the men aged 75 years and over were pipe smokers and 9% cigarette smokers, as compared with 27% pipe smokers and 53% cigarette smokers in those who were less than 75.

TABLE II.—*Smoking Habits by Age Among Men with Cholesterol Assessments*

Type of Tobacco Used	Age in Years			
	Under 75		75 and Over	
	No.	%	No.	%
None ..	26	17	12	23
Cigarette only ..	83	53	5	9
< 20/day ..	45	29	2	4
> 20/day ..	38	24	3	5
Pipe only ..	42	27	35	66
Cigarette and pipe	5	3	1	2
Total ..	156	100	53	100

Relationship Between Serum Lipids and Smoking

The nature of the relationship between smoking and both serum cholesterol and β/α lipoprotein ratio is indicated in Table III. This shows that both measures of serum lipid are just a little higher in non-smokers or very light smokers than in the heavier smokers of cigarette or pipe tobacco. This trend is confirmed by the correlation analysis shown in Table IV, where it

TABLE III.—*Relationship of Cigarette and Pipe Smoking with Serum Cholesterol and β/α Lipoprotein Ratio*

Type of Tobacco Used	Mean Serum Cholesterol (mg.)		Mean β/α Lipoprotein Ratio	
	No.	Mean	No.	Mean
None ..	38	214	36	2·0
Cigarette only; No./day:				
5	12	201	11	2·1
10	34	213	33	1·9
20	33	201	33	1·9
30 and over	8	206	8	1·8
Pipe only; oz./week:				
1	3	203	3	2·2
2	25	197	23	1·7
3	21	213	19	1·9
4	17	211	17	1·8
5 and over	11	219	11	1·7

can be seen that all the coefficients of correlation are negative, but with the exception of β/α lipoprotein ratio in pipe smokers and non-smokers the trends are not statistically significant.

TABLE IV.—*Correlation Between Serum Lipids and Smoking in the Entire Sample*

	Serum Cholesterol (mg. 100 ml.)	Serum Lipoproteins β/α Ratio
Cigarette smokers and non-smokers ..	−0·07	−0·10
Pipe smokers and non-smokers ..	−0·14	−0·33*
Tobacco index	−0·01	−0·11

* $P<0.001$; none of the other statistics are significant at the 5% level.

Bronte-Stewart (1961) believes that the proved relationship between serum cholesterol and cigarette-smoking in younger men may be due to dietary preferences. It is possible that these old people living on pensions cannot afford to smoke heavily and to eat well, and therefore a comparison was made between the dietary indices and some other characteristics of, on the one hand, the heavy smokers of both cigarettes and pipe tobacco and, on the other, the non-smokers (Table V). It can be seen that the heavy cigarette-smokers are significantly younger than the other two groups—a finding which reflects the difference between the smoking habits of the generation which reached maturity before and after 1914. In the sample as a

TABLE V.—*Serum Lipids, Age, and Dietary Index of Non-smokers and Heavy Smokers of Cigarette and Pipe Tobacco*

	No.	Age in Years		Cholesterol (mg.)		β/α Lipoprotein Ratio		Dietary Index	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Non-smokers	38	72·4	5·1	214·5	42·9	2·0	0·4	7·1	3·6
30 cigs./day or more	8	67·7*	1·9	205·7	37·3	1·8	0·3	7·0	2·3
5 oz. pipe tobacco/week or more ..	11	72·3	4·1	216·8	65·0	1·7	0·3	9·4	4·9

* Significantly younger than the other two groups ($P<0.02$); no other group differences are significant at the 5% level.

whole there was a significant negative regression of serum cholesterol with age of 1.7 mg./year (Acheson *et al.*, 1958), but, even allowing for this, the differences between the mean serum cholesterol values are not significant at the 5% level. The dietary index used in this study does not measure preferences, but it has already been shown above that there is reason to believe that it measures the general level of nutrition and therefore would show whether the heavy smokers go without food. The analysis in Table V indicates that this is not the case; indeed the heavy pipe-smokers eat rather more than the non-smokers, although the difference is not quite significant ($t=1.69$; $0.1>P>0.05$).

Discussion

There can be little question of the relationship between serum lipids and cigarette-smoking in middle-aged men. It has been demonstrated in the U.S.A. (Gofman *et al.*, 1955; Thomas, 1958; Dawber *et al.*, 1959), Finland (Karvonen *et al.*, 1959), and South Africa (Bronte-Stewart, 1961); yet in the present data based on old men there is no evidence whatsoever of such a relationship—in fact, there is a suggestion that non-smokers may have a mean serum cholesterol and β/α lipoprotein ratio which are higher than in smokers.

Bronte-Stewart (1961) believes that the reason serum lipids are raised in younger smokers is because taste preferences induce them to eat more cholesterologenic

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substances, such as saturated fats, than non-smokers; he has published some evidence, which he does not claim to be conclusive, to support his view (Bronte-Stewart, 1961; Perrin *et al.*, 1961).

The lack of correlation between serum lipids and smoking habits in the present sample receives indirect support from the fact that smoking does not seem to be associated with coronary heart disease in them (Acheson, 1961) or in two other samples of men over the age of 65 years (Hammond and Horn, 1954; Doll and Hill, 1956). On the present evidence it is not possible to give a reason for this, even less to explain the possibility of an inverse relationship, but several theories suggest themselves. First, as has been stated, limited financial means might have caused those who smoke more to eat less, but in the present sample there was nothing to suggest that means were so limited nor that heavy smokers ate less. Secondly, if we accept Bronte-Stewart's basic hypothesis, it could reasonably be argued that the effect of ageing on the sense of taste may be more powerful than any effect of tobacco-smoking, so that the latter is obscured among old people. Thirdly, it could be that with increasing age the pattern of metabolism of fats and lipids is changed.

Our finding, although difficult to explain, is compatible with our knowledge of the aetiology of coronary heart disease in old men. In younger age-groups the greater part of coronary disease takes the form of infarction caused by thrombotic occlusion of a major vessel, a lesion which has repeatedly been shown to be associated with high serum cholesterol and a raised β/α lipoprotein ratio. Bronte-Stewart (1961) believes that the relationship between cigarette-smoking and such disease is due to the raised serum cholesterol which smokers have, rather than to any pharmacologically induced response smoking may elicit from the cardiovascular system. Only 9%, of the present series had myocardial *infarction*, and in them the serum cholesterol and β/α lipoprotein ratios were raised; the remaining 81%, the majority of whom had angina pectoris and/or myocardial ischaemia, did not differ from the controls in their smoking habits or their serum lipids or serum cholesterol. Dawber *et al.* (1958), in a longitudinal study of younger men, have shown that, although cigarette-smoking and high serum cholesterol predispose to coronary thrombosis, neither predisposes to new cases of coronary heart disease presenting as angina pectoris. In line with this is the failure of Paterson *et al.* (1956) to demonstrate a correlation between cholesterol levels during life and the extent of atherosclerosis at necropsy. Our present finding, therefore, is consistent with the view already expressed (Acheson, 1961) that coronary heart disease which presents as angina pectoris and electrocardiographic evidence of myocardial ischaemia without infarction in old men is of different aetiology from acute coronary thrombosis, which is the more usual form the disease takes in younger men.

Summary

It is shown in a random sample (221) of a defined population of men aged 65-85 years that tobacco-smoking, whether in pipes or cigarettes, is not associated with elevation of the serum cholesterol or the β/α lipoprotein ratio. The significance of this finding in the aetiology of coronary heart disease is discussed.

We are again pleased to acknowledge our gratitude to the directors of Messrs. Arthur Guinness Son and Co. Ltd. (Dublin) to Dr. Brian Pringle and Dr. J. F. Eustace, and to our colleagues in the Moyne Institute, Trinity College, Dublin, for making this study possible. Miss Jane Cooper helped with the computations and Dr. Richard Doll kindly read the text.

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CIGARETTE SMOKING AND SERUM LIPIDS IN YOUNG MEN

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In mortality statistics cigarette-smoking habits have been observed to be correlated with coronary heart disease (Hammond and Horn, 1954; Doll and Hill, 1956; Hammond and Horn, 1958); and the serum lipid level and especially the serum cholesterol and β-lipoproteins are known to be raised in population groups with coronary heart disease. With these facts in mind, many investigators have studied the relationship between cigarette smoking and the serum lipid level (Gofman *et al.*, 1955; Karvonen *et al.*, 1959; Thomas, 1958, 1960; Dawber *et al.*, 1959; Blackburn *et al.*, 1960; Bronte-Stewart, 1961). All these studies support the view that the serum cholesterol level is higher in smokers than in non-smokers. The present communication shows that there was no correlation between smoking habits and serum lipid pattern in a group of young men in Finland.

Material and Methods

The material presented consists of a series of 314 healthy young men who started military service in Finland in 1957–60. The subjects were selected at random. Their mean age was 19.7 years (range 18–25). Blood samples were taken from the cubital vein in the morning after overnight fasting during the first three days of military service. From the specimens the serum total cholesterol (Anderson and Keys, 1956) and the serum total phospholipids (Fiske and Subbarow, 1925) were determined. Serum lipo-protein fractions were separated with the aid of paper electrophoresis, and from the fractions so separated the cholesterol content of the α- and β-lipoproteins was determined. The details and evidence of their accuracy have been presented in a previous study (Konttinen, 1959). Blood-pressure was also measured and relative body weight was calculated according to the Metropolitan Life Insurance Company's (1943) tables. To be sure that the men were healthy, determinations were also made of the blood sedimentation rate and blood haemoglobin level, and the urine was analysed for glucose and protein. Mass x-ray examinations of the chest were also made.

The smoking habits were reported in response to a questionary filled in by each man. There were 145 men who had never smoked. The smokers, divided into subgroups according to daily consumption of tobacco (see Table), had smoked for at least one year before entering military service. The few pipe smokers were not included in the series. Nearly all the smokers smoked American-type cigarettes with or without a filter.

Results

In the different groups the similarity in level of all the lipids studied (see Table) is obvious. Statistically there is no difference between the groups in total cholesterol, β-cholesterol, or phospholipids. Analysis reveals a probable difference ($P<0.05$) in α-cholesterol variance, but this seems not to depend on the smoking, since this difference is between light smokers and non-smokers. On the other hand, between non-smokers and heavy or moderate smokers there appears to be no significant difference in α-cholesterol.

Discussion

In the present study the similarity in serum lipids found in smokers to those found in non-smokers is at variance with the results of previous studies, in all of which the cholesterol level has been stated to be higher in smokers. The material presented here is very similar in all respects except smoking habits. Body build, expressed as relative body weight, was very much the same. The men came from the same parts of Finland and the occupational structure of the different groups was also similar. The blood samples had been taken similarly in the different groups in respect of time and season. The age range of the whole series is quite narrow (18–25 years) and there is very little difference between the groups. As the men were young they had not been smoking very long, although one criterion in selecting them was at least one year's smoking. Karvonen *et al.* (1959), however, observed a higher serum cholesterol level in smokers of all age-groups, except 50–59 years, in West Finland; the youngest age-group in their study was 20–29 years. Gofman *et al.* (1955) found that the difference in serum lipids between smokers and non-smokers was greater in their youngest (20–29) age-group than in the older ones. In the present study the subjects were slightly younger than the youngest age-groups mentioned above. If the explanation for the difference between the observations in the mentioned studies and the present one lies in this point, the effect on serum lipids of exposure to cigarette smoking seems to occur after some years of smoking, but not, however, during so short a smoking period as in the present work.

When considering atherosclerosis many investigators have stressed the importance of the $\beta:\alpha$ ratio in the lipoprotein fractions. It has been noticed that an increase in this ratio is encountered in patients with atherosclerosis (Nikkilä, 1953; Oliver and Boyd, 1955; Jencks *et al.*, 1956). In the studies concerning the correlation between smoking and serum lipids in which lipoprotein fractions are included the $\beta:\alpha$ ratio has been found to be raised in smokers (Gofman *et al.*, 1955; Bronte-Stewart, 1961). In the present study, by contrast, no trend parallel with the smoking habits could be discerned in serum lipid levels.

The serum phospholipids have been shown to have the important function of stabilizing other lipids in solution

Serum Lipids in 314 Young Men Grouped According to Smoking Habits

Group	No. of Cigarettes/Day	No. of Men	Serum Cholesterol (mg. %) Mean ± S.D.	Serum α-Cholesterol (mg. %) Mean ± S.D.	Serum β-Cholesterol (mg. %) Mean ± S.D.	Serum Phospholipids (mg. %) Mean ± S.D.	Relative Body Weight (kg.) Mean	Age (Years) Mean
Non-smokers		145	201.8 ± 32.5	52.8 ± 11.4	151.0 ± 34.8	210.0 ± 34.8	66.4	19.3
Light smokers	1–10	53	206.8 ± 37.0	58.2 ± 9.55	146.6 ± 34.9	222.1 ± 32.5	69.9	19.9
Moderate smokers	11–19	54	203.1 ± 34.5	55.3 ± 11.7	147.9 ± 35.5	224.7 ± 31.0	67.2	20.1
Heavy smokers	20+	62	202.3 ± 32.6	53.7 ± 10.6	144.6 ± 31.1	210.5 ± 24.6	68.2	19.8

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(Ahrens and Kunkel, 1949), and it has therefore been inferred that an increase in the ratio of phospholipids to cholesterol helps to prevent atherosclerosis. This view has been supported by the observation that the phospholipid:cholesterol ratio is smaller in atherosclerosis than in age-matched controls (Gertler *et al.*, 1950; Oliver and Boyd, 1953). The published studies on the relation between serum lipids and smoking do not include reports concerning serum phospholipids. In the present study phospholipids show no trend paralleling the smoking habits.

Attempts have been made to relate the rise in serum lipids observed in the previous studies in smokers to differences in the diet possibly due to smoking. Krut *et al.* (1961) have noted a difference in the perception of bitter taste between smokers and non-smokers. According to those authors this could lead to smokers having a preference for some special foods. The same group of investigators (Perrin *et al.*, 1961) have observed that smokers consumed more fat than non-smokers, but the difference was too small to explain the difference in serum lipids, and in Finland S. Punsar (unpublished data) could not detect any difference between the diet of smokers and that of non-smokers. Even the greater amount of fat consumed by smokers does not necessarily signify that all this fat is absorbed, for a recent study (Konttinen and Rajasalmi, to be published) has shown that the rise in serum triglycerides after a fatty meal is less in heavy smokers than in non-smokers.

The effect of giving up smoking should throw further light on the correlation between cigarette smoking and serum lipids, but in the only relevant report I found in the literature no change in serum cholesterol was detected in the six subjects studied (Thomas and Eisenberg, 1959).

The possibility has also been discussed that smoking could be another manifestation of the disturbance responsible for the rise in the serum cholesterol level, and in this connexion mental tension was incriminated as the cholesterol-elevating factor (Thomas and Murphy, 1958; Wertlake *et al.*, 1958; Grundy and Griffin, 1959; Dreyfuss and Czaczkes, 1959; Peterson *et al.*, 1960). It should be remembered, however, that mental tension cannot be measured but only estimated.

It is evident that further investigations of the relationship of smoking to the serum lipids are required.

Summary

Serum total cholesterol and the cholesterol content of the α- and β-lipoprotein fraction and serum phospholipids have been determined in a series of 314 healthy young men (range 18–25 years) starting military service, grouped according to smoking habits. There were no differences relating to smoking habits in any of the lipids studied.

Addendum.—Since the present study was made Acheson and Jessop (1961) have published their work on serum lipids in old men grouped according to smoking habits. They could find no association between cigarette or pipe smoking and serum cholesterol or β:α-lipoprotein ratio.

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PSYCHO-SOCIAL FACTORS OF SMOKING IN RELATION TO CARDIOVASCULAR DISEASE

Even less conclusive information is available on the role of psycho-social factors of smoking in relation to cardiovascular disease. Studies which have focussed on this are limited in number according to Heinzelmann (44). Even fewer, he found, are those which have specifically examined the relative weight of these variables or their interaction. Reviewing those available, he observes that the evidence is highly fragmentary and uncertain. The findings suggest that the relationship between smoking behavior and coronary heart disease may reflect the influence of stress factors and/or personality mechanisms. However, they permit no definitive statements with respect to the relative role of psycho-social factors and smoking in relation to etiology of the disease.

SUMMARY

Smoking and nicotine administration cause acute cardiovascular effects similar to those induced by stimulation of the autonomic nervous system, but these effects do not account well for the observed association between cigarette smoking and coronary disease. It is established that male cigarette smokers have a higher death rate from coronary disease than non-smoking males. The association of smoking with other cardiovascular disorders is less well established. If cigarette smoking actually caused the higher death rate from coronary disease, it would on this account be responsible for many deaths of middle-aged and elderly males in the United States. Other factors such as high blood pressure, high serum cholesterol, and excessive obesity are also known to be associated with an unusually high death rate from coronary disease. The causative role of these other factors in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them. It is also more prudent to assume that the established association between cigarette smoking and coronary disease has causative meaning than to suspend judgment until no uncertainty remains.

CONCLUSION

Male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance.

(44) Heinzelmann, F. Special report to the Surgeon General's Advisory Committee on Smoking and Health.

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The contents of the Summary and Conclusion have been widely quoted in several publications listed in pages 322 to 343. The Editorial by Hutchison (Bull N Y Acad Med 44: 1471-1475, 1968) is one of a few that has discussed the limitations of the epidemiologic approach. The article is reproduced below.

THE NATURE OF EPIDEMIOLOGIC EVIDENCE: SMOKING AND HEALTH*

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THE SURGEON GENERAL'S REPORT

In 1964 the Advisory Committee to the Surgeon General of the Public Health Service identified a number of disease categories for which the committee was willing to state that a causal association with cigarette smoking had been established.** These were all diseases of the respiratory apparatus, including cancers of the lip, larynx, bronchus, and lung, plus one nonmalignant condition, chronic bronchitis. No cardiovascular diseases were so designated.

A second group of disease categories was identified as associated with cigarette smoking, but a causal relationship was not established. In this group were included arteriosclerotic heart disease and a category referred to as noncoronary cardiovascular disease. The noncoronary category includes endocarditis, hypertensive heart disease, and certain

*Presented at the *Conference on Smoking and the Heart* held by the New York Heart Association at The Waldorf-Astoria, New York, N. Y., March 26, 1968.

**Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, U.S. Department of Health, Education, and Welfare, Public Health Service. Washington, D.C., Govt. Print. Office, 1964.

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residue rubrics of other heart and circulatory disease. In addition to these cardiovascular categories the associated group included cancers of the oral cavity, esophagus, and bladder, and the benign conditions emphysema, gastric ulcer, and cirrhosis.

The judgment relative to coronary disease is somewhat stronger than that relative to other conditions where a causal conclusion was not possible. The committee felt that a prudent course of action with respect to coronary disease should be based on a presumption of a causal association. Countermeasures should not be postponed while further refinement of the evidence is awaited. Subsequent data add strength to these conclusions.

Cause-Effect Concept

The concept of cause that is appropriate to discussions of the relation of smoking to illness should be considered here.

I should like to distinguish two concepts which I shall call the pragmatic concept and the elaborated theory concept. Under the pragmatic concept a cause-effect relation exists when *deliberate manipulation* of a series of preliminary alternatives is followed by a *statistically predictable variation* in a second series of alternatives. The preliminary manipulation is referred to as the cause, and the outcome in the second series is referred to as the effect. In the present discussion a pragmatic cause-effect would be proved if an investigator were to manipulate the smoking habits of a group and if the predicted incidence of disease was to follow. It should be noted that this concept does not involve either a necessary or sufficient relation. To say that smoking causes coronary disease permits the possibility that coronary disease occurs in some frequency in the absence of smoking. It also permits the possibility that some smokers, or even most smokers, will not develop coronary disease. This concept says nothing about the mechanism of the causal association. Finally the concept is of direct significance for public health action, since it indicates that a certain manipulation will improve health in some measure.

Under the elaborated theory concept a cause-effect relation is established by demonstrating that the relation is a consequence of laws of basic science. The emphasis is on mechanism. The relation must generally be stated in much more refined terms than "smoking" and "coronary disease." For example, it may be concluded that nicotine stimu-

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lates or paralyzes certain ganglia with a consequent alteration in pulse rate. This alteration may be inconsequential in normal hearts but may set off a further chain of events in hearts with previously damaged coronary arteries. The ultimate conclusion will be that smoking is followed by coronary heart disease under conditions that the smoke includes nicotine, the smoke is inhaled in specified concentrations, and the heart is previously damaged in some specified way.

A portion of the disagreement in the literature and in meetings such as this arises from a misunderstanding of which of these two cause-effect concepts is under discussion. A greater disagreement, however, rests on a judgmental decision as to what evidence is necessary to accept either concept.

Epidemiologic Evidence

An extensive literature on associations between smoking and cardiovascular disease is now available. I propose to comment on some of the studies in this literature in which the unit of observation is a person and in which information is collected to characterize persons as to state of health. These are the studies which are commonly referred to as epidemiologic studies. When these studies are interpreted in terms of cause-effect relations the cause-effect concept is usually the pragmatic one.

The proof of cause-effect would be established or rejected by deliberately manipulating the smoking habits of such persons and observing the results. No such studies have been made to my knowledge. Controversy, when it occurs, rests on differences of opinion as to what constitutes proof in the absence of such a manipulative study. There are those who feel that proof is *never* established without such human experimentation. Others feel that proof can be established through observational studies, but there is little agreement as to what sorts of observations are required.

A number of schemes have been suggested for assuring such proof. Koch's postulates are an early attempt, but are applicable only when the causative event is exposure or nonexposure to living organisms. The surgeon general's committee has proposed a number of conditions which must be satisfied. These include consistency, strength, specificity, and coherence of the association. The ultimate decision, however, is said to be judgmental.

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In general the acceptability of proof depends on the degree to which observations may be said to mimic the manipulative experiment. Perhaps the best example of such a "natural experiment" is the study that demonstrated a leukemogenic effect of ionizing radiation in the survivors in Hiroshima.

Smoking and Cardiovascular Disease

There is no study of smoking effects which closely resembles this sort of natural experiment. In all available studies persons are characterized as nonsmokers, former smokers, light smokers, heavy smokers, inhalers, and as other descriptive types with respect to the smoking habit. There is no presumption that the assignment to such a category was a chance event, and indeed some investigators have made it clear that the decision to smoke is not a chance event but is to a degree predictable on the basis of characteristics present before the decision is made, on the so-called constitutional characteristics.

We have then associations between smoking and certain cardiovascular diseases that are technically and statistically satisfactory, in the sense that they would rarely occur by chance in our samples if, in fact, smoking had nothing to do with these diseases. We have also associations between certain constitutional factors and smoking, also technically satisfactory. We may think of three possible explanations. First, the constitutional factors may lead to both smoking and disease. Second, smoking may cause disease. Third, disease may cause smoking. These three explanations may all be in effect.

If the constitutional association were a very strong one, so that all or almost all smokers and nonsmokers could be identified by eye color, for example, then we could not support the cause-effect hypothesis. But in fact the constitutional association leaves much room in which to maneuver. We can find, for example, smokers and nonsmokers within both vulnerable and nonvulnerable constitutional types.

When the diseases which are accepted by the committee as causally related are studied it is found that the relative risk is very high, often of the order of 10 to 20. This in essence means that if the cause-effect explanation is correct, it accounts for a very large part of these diseases. For example, it is possible to suppose that most lung cancer may be due to smoking and would be abolished by the cessation of smoking. With the doubtful group, relative risks of the order of 1.5 to

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3 are found, and smoking, if causal, can be incriminated in only a small portion of the cases. No one can suppose that the abolition of smoking would wipe out cardiovascular disease or even a very large part of it.

This low relative risk is no argument against the cause-effect hypothesis, but it does make it difficult to give convincing proof of the hypothesis. It opens the possibility that whatever factors cause the majority of these diseases are also responsible for the association with smoking. In the case of lung cancer many of us find it hard to believe that we could have overlooked some confounding variables that are so highly correlated with both smoking and lung cancer. With cardiovascular disease there is the troublesome suspicion that some relatively low-level association really may have been overlooked.

The strongest argument derived from epidemiologic studies in favor of the causal interpretation with respect to coronary disease is the finding that the risk diminishes with time after smoking is abandoned. It should be noted that this by no means decides the debate. It may be hypothesized that the constitutional tendency to smoke also governs the length of time a consumed individual can stay away from the habit. Those who manage to stay away for periods of 5 to 10 years may be supposed to have a low level of constitutional vulnerability to smoking.

As the evidence has accumulated in recent years, the complexity of the hypotheses necessary to contradict the causal hypothesis has increased. It is in evaluating the acceptability of these complex arguments that judgment must play the final role. It is unlikely that all informed scientists will come to the same judgment and decision when studying the same body of data. This will probably dismay many lay people, but it is a phenomenon with which scientists should be familiar. It should not be a cause for despair or distrust among scientists. Finally, it should be possible, as the surgeon general's committee has done, to recognize the point when evidence is adequate to support public health action even though it is not adequate to consider an issue closed.

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The Health Consequences of SMOKING

A PUBLIC HEALTH SERVICE REVIEW : 1967

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

PART II

Technical Reports on the Relationship of Smoking to Specific Disease Categories

CHAPTER 1

Smoking and Cardiovascular Diseases

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SMOKING AND CORONARY HEART DISEASE

Coronary Heart Disease Mortality[1]

The relative importance of the association between cigarette smoking and coronary heart disease (CHD) as compared to the association of smoking with other diseases was previously described in the introduction to chapter 11 of the Surgeon General's 1964 Report.

In the United States more persons die from coronary heart disease than from any other single cause; and this most common form of fatal cardiovascular disease accounts for a greater percentage of excess deaths among cigarette smokers than do deaths from lung cancer. In 1964, there were 1,798,000 deaths from all causes, of which almost 545,500 or 30.3 percent, were due to atherosclerotic heart disease, including coronary heart disease. Table 1 gives the 1964 death rates for *coronary heart disease* per 100,000 persons by age and sex:

TABLE 1.—*1964 death rates for coronary heart disease per 100,000 persons by age and sex*

	All ages	25-34	35-44	45-54	55-64	65-74	75-84	85+
Both Sexes	253.1	6.9	53.2	203.8	576.3	1,284.9	2,937.7	6,852.9
Males	354.2	11.0	90.9	341.3	850.8	1,942.4	3,623.0	7,400.4
Females	213.5	3.0	17.4	76.3	259.4	926.5	2,464.0	6,550.0

SOURCE: National Center for Health Statistics [97].

These data illustrate the dramatic increases in the risk of death from coronary heart disease as age advances. For males the rates among persons over the age of 45 appear to double from one decade to the next; among females the increased risk of death with advancing age is more dramatic—a threefold increase every 10 years. Of perhaps greater importance are the relatively low death rates among females, particularly below the age of 65, compared to males of comparable age. The mortality differential between the sexes becomes less as age advances; under 45 years of age the coronary death rate among men is five times as high as among women and in the 75–84 year age group it is only about 1.5 times as high.

The Surgeon General's 1964 Report determined a median mortality ratio (*99*) (pp. 103–110) for coronary heart disease of male current cigarette smokers of 1.7. Since this report, five large prospective studies of smoking and mortality have been updated on the basis of longer periods of observation on each study subject. Current findings are therefore more definitive and permit more detailed analysis of the interrelationship of cigarette smoking to other significant variables such as age, sex, and the nature of the smoking habit in terms of amount and duration of smoking. Pertinent findings are presented below from the studies of veterans in the United States (*52*) and Canada (*14*) and the extensive data reported by Hammond (*47*), Doll and Hill (*25, 26, 27*), and Borhani (*17*).

The relative excess mortality associated with cigarette smoking is generally expressed in terms of a mortality ratio. This statistic is defined as the ratio of the number of observed deaths among smokers, to the expected deaths among smokers, if the age-specific mortality rates observed among non-smokers had prevailed (*52*). The process of computing the expected number of deaths among smokers takes into account and adjusts for any differences in the age distribution of the smokers and the nonsmokers under observation. Generally smokers are defined as persons currently smoking cigarettes, and nonsmokers as those who never smoked or who never smoked regularly.

Table 2 shows the mortality ratios for coronary heart disease deaths among current cigarette smokers according to the amount smoked daily in U.S. and Canadian male veterans.

TABLE 2.—*Coronary heart disease mortality ratios, age-adjusted among current cigarette smokers by amount smoked daily*

	Cigarettes smoked daily				
	Under 10	10-20	21-39	More than 39	40+
U.S. male veterans	1.3	1.7	1.8	.....	2.0
Canadian male veterans	1.6	1.6	.....	1.8	.....

SOURCE: U.S. veterans study (52) and Canadian pensioners study (14).

In both studies (*14, 52*) the mortality ratios were similar and increased with increasing intensity of cigarette smoking. Slightly higher ratios are reported in the U.S. veterans study for current smokers of cigarettes only.

[1] All death rates throughout this chapter are per 100,000 population, unless otherwise indicated.

(97) U.S. PUBLIC HEALTH SERVICE. National Center for Health Statistics. Mortality from diseases associated with smoking: United States, 1959–61. Washington. U.S. Department of Health, Education, and Welfare. Vital and Health Statistics Series 20, No. 4, Public Health Service Publication No. 1000, October 1966. 45 pp.

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(25) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors (pt. 1). British Medical Journal (London) 1(5395): 1399–1410, May 30, 1964.

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(27) DOLL, R., HILL, A. B. Mortality of British doctors in relation to smoking: Observations on coronary thrombosis. *In:* Haenszel, W., Editor, Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 205–268.

(17) BORHANI, N. O., HIGHTOWER, H. H., BARSLOW, R. Report of a 10-year follow-up study of the San Francisco long-shoremen. Mortality from coronary heart disease and from all causes. Journal of Chronic Diseases (St. Louis) 16: 1251–1266, 1963.

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The statistical methods which appeared in the 1964 report, reappear in the 1967 one. A second article criticizing the methods is appended (from the Bulletin of National Statistical Institute, pp 856-860, 1966).

A CRITIQUE ON THE REPORT OF THE SURGEON GENERAL'S ADVISORY COMMITTEE ON SMOKING AND HEALTH

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ABSTRACT

The Report of the Surgeon General's Advisory Committee on Smoking and Health was first issued in January 1964 by the United States Public Health Service.

The critique submitted for presentation by the author is only part of a much longer version. In other words, the Report of the Surgeon General's Committee lends itself to a considerable amount of discussion.

Are the conclusions of the Surgeon General's Committee justified? The author feels that they are not and he bases that opinion on an examination of the methods employed by the Committee in arriving at its conclusions, the character of the Report itself and the composition of the Committee as far as scientific disciplines are concerned. In that respect, his critique can be summarized as follows:

1. In its Report, the Surgeon General's Committee did not make a clear distinction between *causal significance* and *proof* and, on one occasion, did use the terms interchangeably.

2. It organized the evidence poorly, so poorly, that it is not difficult for one, in reading the Report, to lose sight of tee objectives.

3. It did not use a systematic approach in investigating various aspects of the problem.

4. It failed frequently to offer reasonable or meaningful derinitions of statistical and epidemiological terms. An outstanding example of this is given on page 3 of the critique.

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5. It was not altogether consistent in applying principles.

6. Its criteria for judging causation were not entirely realistic. In fact, with one exception, those criteria could be better described as criteria for ascertaining the value of a variable as a *diagnostic index*, a *predictor*, or both.

7. It engaged in a considerable amount of rationalization with respect to evidence which did not conform to the particular hypothesis which it had chosen to explore in detail. On the other hand, it appeared to be more convenient for the Committee to downgrade evidence which was consistent with another hypothesis than for it to change its policy and explore that hypothesis in detail as well.

8. Its Report is replete with redundancies. Indeed, there are instances in which the paraphrasing is such that one is left with the impression that new pieces of evidence were being introduced.

9. It did not distinguish between *primary* and *secondary* cancer of the lung, and such a distinction is essential, since cigarette smoking or not smoking is not assumed to be related to the occurrence of secondary cancer of the lung.

10. Not all pertinent scientific disciplines were represented on the Committee. For example, there was no psychiatrist, psychologist, sociologist, geneticist or radiologist on the Committee.

11. The Committee did not appear to be consistently aware of the fact that *self-selection* is the one known *factor* which cannot be controlled completely in any survey regardless of form. Self-selection may be characterized in the following hypothesis:

Even if cigarette smokers, as a group, did not smoke, there still would be a higher proportion of persons with *primary* cancer of the lung, say, among them than among non-smokers, as a group, since constitutionally they are more disposed to the disease. That, of course, is a statement of the *constitutional hypothesis*.

By taking all of these criticisms and others into consideration, and by exploring the constitutional hypothesis in much greater detail than did the Surgeon General's Committee, the author is able to conclude that there is strong reason to believe that the evidence appearing in the Report of the Surgeon General's Committee fits the *constitutional hypothesis* at least as well as it does the *cigarette hypothesis*. That alone would suggest that a causal significance cannot be attached to the relationships mentioned at the outset of the critique, i.e., to the relationship between cigarette smoking or not smoking and the occurrence of certain respiratory diseases and to the relationship between cigarette smoking or not smoking and the occurrence of coronary heart disease. (It is not feasible to conduct studies of the type which would force these relationships to disappear if they are not those of cause and effect). Finally, more research would be necessary to test *definitively* the strength of one hypothesis against that of the other, and that is how the author feels the situation with respect to smoking and health stands at the present.

DISCUSSION

W. G. COCHRAN. As the statistician on the Committee whose report Dr. Saiger has criticized, I am a little hesitant to enter the discussion. The Committee studied the evidence for a year, with great assistance from a large panel of expert consultants. The Committee's report has 387 pages, and received widespread distribution and publicity. Consequently, there is merit in the point of view that the Committee has had its say, and that when critiques appear, the interested bystander can read the critique and the Report and form his own opinion.

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Further, the problem of the relation between smoking and health is one on which new data are continuously accumulating, particularly data on females, of which relatively little was available to the Committee, and further person-years of experience in the prospective studies, which facilitate the type of control on more variables that Dr. Saiger and I both favour. The most interesting question is not what the state of the evidence was early in 1963, when the Committee study was in progress, but what it is now. This, of course, gets beyond the scope of Dr. Saiger's paper.

Nevertheless, I would like to comment, for two reasons. Dr. Saiger's references to the Committee's work are inaccurate in a number of respects. I would like to quote two examples, to reinforce my hope that those who are interested in his arguments will read the relevant part of the report. Secondly, the problem of appraising the self-selection or constitutional hypothesis — the main theme of Dr. Saiger's paper — is a challenging one for statisticians.

First as regards inaccuracies. On pp. 6—7 Dr. Saiger doubts the competence and ability of the 10 men, and particularly of the poor statistician, to cover the vast literature on this problem in the time used. He omits to tell you of the 189 persons and agencies used as expert consultants, through these are listed and their contributions described right at the beginning of the Report.

At the top of page 3, Dr. Saiger refers to the committee's definition of a cause as being "a significant, effectual, relationship between an agent and an associated disorder or disease in the host", and proceeds to ridicule such a definition. In fact, the Committee gave no formal definition of a cause, recognizing that cause and effect are complex ideas, but instead discussed on pp 20—21 their conception of causality. The sentence from which Dr. Saiger purports to be quoting reads as follows (p.21). "The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host". The Report goes on at once to state: "no member of this Committee used the word *cause* in an absolute sense in the area of this study" and "all members shared a common conception of the multiple etiology of biological processes".

As regards the self-selection hypothesis, I agree with Dr. Saiger that a well-planned, long-term randomized experiment would be enlightening but is impracticable. In appraising this hypothesis from non-randomized data, what can one do? To quote some of the statistical evidence for males, the death rate at a given age increases steadily with the number of cigarettes smoked. For men of a given age who report smoking the same amount, the death rate increases with the number of years smoked. For men of a given age who previously smoked a given amount, the death rate is lower for those who have stopped than for those who have continued. In two groups of men of the same age who have stopped for the same length of time, the group which previously smoked more have the higher death rate. Dr. Saiger seems to think that the self-selection hypothesis can comfortably accomodate all these results and others which I could cite. My opinion is that it is being stretched very thin.

Secondly, one considers all studies in which differences in physique, habits, ancestry, psychological pattern and so on between cigarette smokers and non-smokers have been examined. Dr. Saiger mentions, as does the Report, a number of variables in which differences have been found in some studies. However, these differences are at most small differences between the means of two populations that overlap extensively.

Thirdly, in the prospective and retrospective studies, one adjusts for any variables other than smoking that are known or suspected to be related to the probability of dying. In the analyses leading to the Report, these adjustments were computed wherever the data allowed it. Except for age, for which adjustment is essential, these computations produced only slight changes in the mortality ratio. On page 13, in mentioning a seven — variable adjustment by Hammond, Dr. Saiger points out that the 7 did include important variables such a longevity of parents and grandparents, initial health status of the subject, marital status, and so on. Actually, Hammond already examined the effects of adjusting for each of these variables individually, again finding only slight changes in the mortality rbtio. From inspection of Hammond's data, my judgement was and is that the combination of variables would give essentially the same conclusion.

From all this, the Committees reached the judgement that self-selection could account for only a minor fraction of the observed difference in death rates. It felt in no position to put a precise figure, say 5% or 15%, on this fraction, and like Dr. Saiger, I look forward to seeing more data bearing on the constitutional hypothesis. I feel, however, that the extreme form of the constitutional hypothesis cannot be appraised by these methods. No matter for how many variables we adjust, the objection can be raised that the difference in death rates is due to some further variable not yet measured.

Finally, my opinion is that the new data that I have seen since 1963 do not weaken the main conclusions of the Report.

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V. G. PANSE. A sample survey cannot provide rigorous evidence of cause and effect relationships, irrespective of how many variables are controlled, since factors affecting observed phenomena are almost innumerable. At best, the results can indicate possible lines for further investigation. Some years back Prof. Fisher offered the hypothesis that persons who were genetically more prone to cancer developed a craving for smoking. Neither this nor any other hypothesis can be tested by sample survey. It requires experimentation by randomization of experimental units. Since this does not seem feasible when dealing with human beings, data obtained from experiments on laboratory animals should be very valuable ancillary evidence. Correlations observed in sample surveys should not be taken for cause and effect relationships but as indications which can be tested unequivocally only by experimentation.

G. L. SAIGER. Thank you, Prof. Cochran, for your comments. These are my comments in turn:

1. I should like to urge those who are interested in the problem of whether or not smoking affects health adversely to read the full text of my critique as well as the Report of the Surgeon General's Committee. One ought not to consider my summary, Prof. Cochran's comments and my rebuttal sufficient for the purpose of forming an opinion of his own.

2. Additional evidence *has* accumulated since the Report of the Surgeon General's Committee was first issued. That evidence cannot alter the methods employed by the Committee in arriving at its conclusions, the character of the Report itself nor the composition of the Committee as far as scientific disciplines are concerned. Depending on its quality, I am willing to accept the evidence on which the Report was based and the new evidence for the purpose of testing the strength of the cigarette hypothesis against that of the constitutional hypothesis. I am convinced that all such evidence, old and new, fits the constitutional hypothesis at least as well as it does the cigarette hypothesis.

In speaking of new evidence, Prof. Cochran fails to mention those studies whose results suggest that, exclusive of changes brought about by the disease itself, persons with cancer of the lung have characteristics which are not the same as those of other persons. That is important, since we already know that cigarette smokers differ from non-smokers constitutionally.

3. Prof. Cochran speaks in generalities about alleged inaccuracies in my critique with respect to the work of the Committee, and then proceeds to give examples of two:

a) It should be emphasized that the number of articles and other sources of information which the Surgeon General's Committee was reported to have reviewed exceeded 10 000, and most of the evidence contained in those articles and other sources of information was statistical in nature. Prof. Cochran states that 189 persons and agencies were used as expert consultants by the Committee. As far as I can determine, there were only 31 statisticians in that group, and not all of them would be classified as experts. Though Prof. Cochran had not expressed an opinion publicly on the problem of whether or not smoking affects health adversely before being called on to assist in weighing the evidence, can the same be said of the statistical consultants? My point is this: Some of the statistical evidence contained in the Report of the Committee is not the kind of evidence which a man without bias and of Prof. Cochran's competence would have accepted, I am certain, had he ascertained the value of that evidence himself.

b) Prof. Cochran claims that the Surgeon General's Committee gave no definition of "a cause". To support that claim, he refers to the following sentence on page 21 of the Report of the Committee:

"The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host".

There is no doubt in my mind but that "a significant, effectual, relationship between an agent and an associated disorder or disease in the host" *is* the Committee's definition of "a cause", however Prof. Cochran may choose to interpret it. Obviously, such a definition deserves to be ridiculed. Obviously, such a definition needs to be qualified, and the Committee did that, at least in part, by stating that it did not use the word "cause" in an absolute sense and by expressing a concern for the concept of multiple causation.

4. Indeed, I do feel that evidence acquired in epidemiological surveys and appearing in the Report of the Surgeon General's Committee *is* consistent with the constitutional hypothesis. May I quote from pages 11 and 12 of my critique with respect to that hypothesis:

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From page 11—

"... Once a person's constitution is determined, so are his degree of disposition to the practice of cigarette smoking and his degree of disposition to the disease, and those degrees are highly and *positively* correlated".

From page 12—

"A low degree of disposition to the practice would be exemplified by the person who discontinues it freely after starting late in life and smoking two or three cigarettes per day for two years without inhaling".

That the Committee was confused with respect to the concept of "degree" as opposed to the concept of "kind" is well illustrated on page 10 of my critique. May I quote further:

"... The Surgeon General's Committee assumed that two distinct makeups were required to explore the constitutional hypothesis, one for cigarette smokers and one for non-smokers. But that assumption is neither realistic nor consistent with other observations on constitution made by the Committee. For example, the Committee did not expect to find all males among cigarette smokers and no males among non-smokers. Yet sex is a constitutional factor. In a similar fashion, it should not have expected to find all neurotics in one group and no neurotics in the other, nor even a much higher proportion of neurotics in one group than in the other".

5. Prof. Cochran states that constitutional differences between cigarette smokers and non-smokers are at most small differences. Presumably, he derived that opinion from an examination of single variables. It is not unusual, with biological variables, to observe a considerable amount of overlapping of distributions. I already have alluded to that possibility in the preceding paragraph. Furthermore, I was able to increase estimated distances between the groups significantly by forming combinations of variables. That was one basis for the statement in my critique that constitution more adequately would be represented by a combination of variables. That was one basis for the statement in my critique, and in my summary, that it appeared to be more convenient for the Surgeon General's Committee to downgrade evidence which was consistent with another hypothesis than for it to change its policy and explore that hypothesis in detail as well.

And what does the Report of the Surgeon General's Committee show? It shows that longevity of parents and grandparents could have an appreciable effect on the overall relative risk of dying among cigarette smokers, and that health status of the subject at the beginning of the survey, marital status, whether or not tranquilizers were being used and degree of exercise are highly related to the probability of dying, i.e., they are known *factors* of importance in the occurrence of death. It also shows that Hammond did not include those factors in a combination. Prof. Cochran confirms that observation in his comments.

Hammond did include other factors in a combination, however, and his results indicate that age and sex are not the only factors which should be controlled in exploring the constitutional hypothesis. (Note: The Surgeon General's Committee controlled age and sex only in arriving at its relative risks). Prof. Cochran and I both agree that studies should be conducted in the area of controlling progressively larger combinations of variables. The constitutional hypothesis does not specify that, in epidemiological surveys, the point can be reached where the relative risks of dying would estimate unity. (The only way in which self-selection can be controlled completely is by means of a long-term human experiment). There is a strong possibility, however, that they would approach unity. If they did, then the conclusions of the Surgeon General's Committee would be weakened further rather than strengthened. Therefore, the statement by Prof. Cochran that "no matter for how many variables we adjust, the objection can be raised that the difference in death rates is due to some further variable not yet measured" is grossly misleading. For the same reason, I cannot agree with Prof. Cochran that the problem of exploring the constitutional hypothesis is a challenging one for statisticians.

6. There is an important piece of evidence which Prof. Cochran, as a member of the Surgeon General's Committee, fails to explain: Why is it that primary cancer of the lung, histologically similar to that found in humans, can be produced in animals and with a variety of substances, but, as far as is known, not with condensates of cigarette smoke?

Prof. Cochran's comments and my rebuttal may have created some misunderstanding. Therefore, in closing, let me state my position as follows:

I am not an advocate of the constitutional hypothesis. The chief purpose of my critique is to determine whether or not the conclusions of the Surgeon General's Committee are justified. In examining the methods employed by the Committee in arriving at its conclusions, I find that it should have explored more than one hypothesis in detail and I offer, as a logical alternative, the constitutional hypothesis.

Though Prof. Cochran and I disagree on many points we apparently do not disagree on an important one, namely on the need for more research to test further (or *definitively*, as I call it) the strength of the cigarette hypothesis against that of the constitutional hypothesis.

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The U.S. veterans study also permitted the comparison of age-specific coronary heart disease mortality rates for ex-smokers and current cigarette smokers (table 2A). From these data, it appears that cessation of cigarette smoking is followed by a reduction in risk of coronary heart disease mortality as compared to those who continue to smoke cigarettes.

TABLE 2A.—*Annual death rate per 100,000 from coronary heart disease by age, cigarette-smoking status and number of cigarettes smoked per day, U.S. veterans study*

Number smoked per day[1]	45-64		55-64		65-74	
	Current cigarette smokers	Ex-smokers[2]	Current cigarette smokers	Ex-smokers[2]	Current cigarette smokers	Ex-smokers[2]
1 to 9	195	125	594	432	1,374	1,105
10 to 20	297	133	830	557	1,577	1,260
21 to 39	390	57	912	743	1,701	1,366
40+	502	.....	1,101	646	1,955	1,452

[1] This is the current rate of smoking for current cigarette smokers and the maximum rate attained for ex-cigarette smokers.
[2] Ex-smokers who stopped for reasons other than doctor's orders.
Source: U.S. veterans study (12).

The Hammond study findings summarized in table 3 are based on coronary heart disease deaths reported over a 4-year period among approximately 1 million persons (441,000 men and 563,000 women).

TABLE 3.—*Coronary heart disease mortality ratios among current cigarette smokers only, by amount smoked daily*

Age and sex	Non-smokers	Cigarettes smoked daily			
		Under 10	10-19	20-39	40+
Men:					
45 to 54	1.0	2.4	3.1	3.1	3.4
55 to 64	1.0	1.5	1.9	2.0	2.1
65 to 74	1.0	1.3	1.6	1.6	(1)
75 to 84	1.0	1.2	1.4	1.1	.....
Women:					
45 to 54	1.0	0.9	2.0	2.7	.....
55 to 64	1.0	1.3	1.6	2.0	.....
65 to 74	1.0	1.1	1.4	1.9	.....
75 to 84	1.0	.....	.....	.....	.....

[1] Expected deaths were less than 10.
Source: Hammond, E. C. (17).

Tables 3 and 4 show that both men and women who smoke cigarettes have relatively higher death rates from coronary heart disease than nonsmokers, although men have higher rates than women. For each sex and for each age group, the mortality ratios for coronary heart disease generally increase with increased intensity of cigarette smoking (table 3). The highest mortality ratios for both men and women are observed in the 45-54 year age-group; the coronary heart disease death rates among heavy smokers in this age group are three times the death rates for nonsmokers for both sexes. The mortality ratios for both men and women decrease with advancing age in each intensity category. This trend may reflect the effects of selective survival of smokers who have survived the elevated risks at younger ages of coronary heart disease and other diseases associated with cigarette smoking.

Another explanation of the decrease in mortality ratios with aging is that the effect of smoking, while substantial in increasing death rates, cannot be expected to be proportionate to all other causes of coronary heart disease as age advances. Considering the advanced degree of atherosclerosis generally found among nonsmokers over age 65, the deleterious effect of smoking is more appropriately represented by the excess in death rates among smokers. Table 4 below shows the observed death rates from coronary heart disease among persons studied by Hammond and classified by age, sex, and smoking status. Although the mortality ratios decreased with age, differences in death rates, which reflect the numbers of persons who die in each age group, increase. This could be interpreted to mean that, although relative to other factors, the role of cigarette smoking tends to diminish with advancing age, the number of excess deaths per 100,000 smokers continues to rise with advancing age.

TABLE 4.—*Age-specific death rates from coronary heart disease per 100,000 persons by age, sex, and smoking status*

Age and sex	Smokers of cigarettes only	Nonsmokers	Excess rate among cigarette smokers[1]	Mortality ratio
Males:				
45 to 54	422	150	272	2.
55 to 64	996	542	454	1.
65 to 74	2,025	1,400	625	1.
75 to 84	3,871	3,132	739	1.
Females:				
45 to 54	66	33	33	2.
55 to 64	275	163	112	1.
65 to 74	941	653	288	1.
75+	2,349	1,973	376	1.

[1] Calculated from the data.
Source: Hammond, E. C. [(17), p. 143.]

The relative decrease in death rates from coronary heart disease associated with the cessation of cigarette smoking is illustrated in table 4A.

TABLE 4A.—*Coronary heart disease (men). Age-standardized death rates for ex-cigarette smokers with history of cigarette smoking only, by former number of cigarettes smoked per day and years since last cigarette smoking. Death rates for current cigarette smokers with history of cigarette smoking only and men who never smoked regularly are shown for comparison. Men aged 50-69*

Ex-cigarette smokers (years since last cigarette smoking)	Smoked 1-19 cigarettes a day			Smoked 20+ cigarettes a day		
	Number of men	Number of deaths	Death rate	Number of men	Number of deaths	Death rate
Under 1 year	749	27	[1] 1,005	2,244	77	[1] 1,070
1 to 4 years	1,844	51	718	5,435	195	1,003
5 to 9 years	1,770	45	725	5,803	152	732
10+ years	4,200	84	403	8,142	206	670
Total ex-smokers	8,569	210	635	21,624	630	813
Current cigarette smokers	22,809	781	947	56,558	1,895	1,020
Never smoked regularly	55,728	1,114	502	55,728	1,114	502

[1] Four or more but less than 10 deaths expected in some of the component 5-year age groups.
Source: Hammond, E. C. [(17), p. 144]

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Source: https://www.industrydocuments.ucsf.edu/docs/jslk0000

Doll and Hill

In a prospective study by Doll and Hill (27) of mortality among British physicians whose smoking habits had been previously recorded, there were 1,369 deaths in the course of 10 years in which the underlying cause was coronary heart disease (27, table 1). The physician population under observation totaled 320,185 person-years. The CHD deaths were classified into three major subcategories: Group 1, comprising 35 CHD deaths in which an associated condition related to smoking, e.g., lung cancer, was recorded on the death certificate; Group 2, comprising 721 CHD deaths in which no other significant contributory cause of death was recorded on the death certificate; and Group 3, comprising 613 CHD deaths which were associated with some other contributory cause, including conditions known to predispose to coronary heart disease, e.g., hypertension, diabetes, and obesity. The CHD death rates for smokers and nonsmokers based only on Group 1 deaths, while subject to large variation, show the largest differentials (data not shown). Among smokers of 25 or more cigarettes daily, the age-adjusted CHD death rate was nearly eight times that in nonsmokers.

Based on Group 2 coronary heart disease deaths, presumably uncomplicated by any other significant disease, the mortality ratio of age-adjusted death rates among continuing cigarette smokers to nonsmokers is found to be 1.6, and for heavy smokers to nonsmokers the ratio is 2.0. However, as shown in table 5, the mortality differentials between smokers and nonsmokers are much larger at the younger ages.

TABLE 5.—*Mortality ratios for different types of coronary heart disease by smoking habits*

Age group	Group 2[1] CHD			Group 3 CHD		
	Nonsmokers	Continuing cigarette smokers		Nonsmokers	Continuing cigarette smokers	
		All amounts	25 or more per day		All amounts	25 or more per day
35 to 44	1.0	4.7	9.7	(2)	(2)	(2)
45 to 54	1.0	3.8	3.5	1.0	1.1	1.7
55 to 64	1.0	1.4	1.6	1.0	1.4	1.9
65 to 74	1.0	1.4	1.8	1.0	1.4	.8
75 to 84	1.0	1.1	2.0	1.0	.8	.2
85 plus	1.0	1.0	(2)	1.0	1.4	(2)
Age adjusted—All ages	1.0	1.6	2.0	1.0	1.1	.9

[1] See text for definitions.
[2] Not calculable; no rate for nonsmokers because of so few deaths.
[3] Very few men in this category.

SOURCE: Data in above table based on values from Study of British Physicians. Table 3 (27).

The mortality ratios shown for Group 3 deaths, i.e., CHD deaths accompanied by some other complicating disease, suggest that, for all age groups combined, smokers do not have any special risk to this type of coronary death. However, smokers below the age of 65 appear to be at a somewhat greater risk, while no consistent differentials are observed among persons in the older age groups.

In summary, the study substantiates other mortality studies' findings that CHD mortality ratios (current cigarette smokers vs. nonsmokers) increase with the number of cigarettes smoked daily, that the ratios are highest in the age group 45–54, and that they decrease as age advances. Moreover, smoking apparently is associated with deaths from coronary heart disease among persons free of other serious disease states.

In a prospective study of California longshoremen, Borhani (17) reported on the mortality experience of more than 3,700 men observed for 10 years. Table 6, derived from his data, provides some additional insights on both the independent and the interaction effects of cigarette smoking.

Men 45–64 years of age who were heavy smokers experienced higher death rates from coronary heart disease than did nonsmokers independent of whether they were hypertensive or nonhypertensive.

TABLE 6.—*Mortality ratio from coronary heart disease among male hypertensives and nonhypertensives by smoking history and age*

Age group	Blood pressure status[1]	Nonsmokers[2]	Heavy smokers[3]
45 to 54	Nonhypertensive	1.0	2.2
	Hypertensive	2.5	9.6
55 to 64	Nonhypertensive	1.0	5.8
	Hypertensive	5.9	9.4

[1] Hypertensives are defined as those having systolic blood pressure of 160 mm. Hg or over or diastolic blood pressure of 95 mm. Hg or over. Nonhypertensives have systolic blood pressure less than 160 mm. Hg and diastolic blood pressure less than 95 mm. Hg.
[2] Nonsmokers in this purpose are defined as those not smoking any cigarettes or less than 20 cigarettes per day. Smokers are those who smoke 20 or more per day.

SOURCE: Borhani, N. O., et al. (17).

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Source: https://www.industrydocuments.ucsf.edu/docs/jslk0000

Prospective Study of British Physicians. The original articles of Doll and Hill contain important details which have been omitted from the 1967 document. Table 5 has grouped all amounts of cigarette smoking, whereas the original articles have specified the quantity from 1 to 14, 15 to 24 and 25+ cigarettes. "There is no clear gradient with number of cigarettes smoked" quoting from (25, 26) Doll and Hill.

Alternatively, cigarette smoking and coronary thrombosis may be related to one another only indirectly through some other factor. It may be, for example, that men with a raised serum cholesterol or of a particular physical constitution (Seltzer, 1963) or who tend to take little physical exercise also tend to take up cigarette smoking, and that these factors contribute to the production of the disease. Such a hypothesis is not, at first sight, unattractive, since the ratio of the mortality rate of smokers to non-smokers is relatively small. But it becomes difficult to accept when all the evidence is taken into account—namely, the much closer relationship at young ages, the increase in mortality with increased amount smoked, the difference between cigarette and pipe smoking and between inhaling and not inhaling, the reduction in mortality with increasing time after smoking has been stopped, and the many physiological effects of smoking on the cardiovascular system. In short, that cigarette smoking is a cause of coronary thrombosis is not, we think, proved; but it is the most reasonable interpretation of the available facts.

In short, we would conclude from these data that the only cardiovascular cause of mortality to show any association with smoking habits is coronary disease, unrelated to hypertension, and that even here the differences in rates are not very marked. The death rate of all smokers (*4.03*) is 23% higher than that of non-smokers (*3.31*), and this excess appears to be limited to the cigarette smokers (*4.39*, or 33% above the non-smokers, Table 18). There is certainly no clear gradient with number of cigarettes smoked, but the highest mortality is found among the heaviest smokers and there appears to be a fall in mortality on giving up smoking (Table 19). We examine these findings more closely in Table 20, which shows the age-specific death rates from coronary disease. These figures show that a rising gradient of mortality from non-smokers to heavy cigarette smokers is clearly present at ages under 65, doubtful at ages 65–74, and absent at age 75 years and over.

We have not sought clinical information about the large number of deaths in this cardiovascular group and consequently have not felt justified in trying to separate a group of deaths which might be ascribed to "cor pulmonale." We noted earlier that 55 cardiovascular deaths included a reference to chronic bronchitis on the death certificate (coronary thrombosis 24, myocardial degeneration 15, hypertension 2, other heart disease 4, and cerebrovascular accidents 10), and it was shown in Tables 16 and 17 that these deaths were closely associated with smoking. It is possible that in a few of them the primary cause was really chronic bronchitis—particularly perhaps among those attributed to myocardial degeneration or "other heart disease"—and that these constitute another cardiovascular group which is also associated with smoking. On the evidence available, however, this group would not appear to be large enough to have materially affected the results. Possibly most such deaths among doctors are attributed directly to chronic bronchitis.

TABLE 18.—*Standardized Death Rates from Cardiovascular Diseases*

Cause of Death		No. of Deaths	Death Rate per 1,000					
			All Men	Non-smokers	All Smokers	Cigarette Smokers	Mixed Smokers	Pipe or Cigar Smokers
Cerebrovascular accidents	(a)*	462	1·39	1·26	1·41	1·43	1·27	1·44
	(b)†	143	0·45	0·51	0·44	0·50	0·41	0·23
	All	605	1·84	1·76	1·85	1·93	1·71	1·67
Coronary disease	(a)*	1,287	3·97	3·31	4·05	4·39	3·87	3·15
	(b)†	89	0·29	0·30	0·33	0·36	0·37	0·21
	All	1,376	4·26	3·61	4·38	4·65	4·25	3·39
Myocardial degeneration		337	0·97	0·59	1·02	1·01	0·95	1·00
Hypertension		133	0·42	0·45	0·42	0·45	0·35	0·37
Other heart disease		135	0·41	0·41	0·41	0·42	0·43	0·33
Other cardiovascular diseases		135	0·41	0·41	0·41	0·45	0·38	0·35
Nephritis		43	0·13	0·09	0·14	0·14	0·13	0·12
Total		2,769	8·44	7·32	8·61	9·11	8·24	7·23
Total hypertensive		370	1·15	1·26	1·14	1·22	1·17	0·81

*(a) Without reference to hypertension on the death certificate.
†(b) Hypertension referred to on the death certificate.

TABLE 19.—*Standardized Death Rates from Cardiovascular Diseases in Relation to the Number of Cigarettes Smoked*

Cause of Death		Death Rate per 1,000				
		No. of Cigarettes Smoked Daily				Given Up Smoking Cigarettes
		1–14	15–24	25+	All Amounts	
Cerebrovascular accidents	(a)*	1·46	1·43	1·63	1·49	1·42
	(b)†	0·46	0·48	0·54	0·51	0·51
	All	1·93	1·91	2·23	2·00	1·93
Coronary disease	(a)*	4·35	4·28	4·97	4·57	3·73
	(b)†	0·29	0·29	0·18	0·28	0·19
	All	4·65	4·57	5·16	4·86	3·92
Myocardial degeneration		1·10	0·94	0·97	1·07	0·87
Hypertension		0·44	0·45	0·45	0·44	0·40
Other heart disease		0·32	0·39	0·21	0·41	0·41
Other cardiovascular diseases		0·41	0·45	0·42	0·54	0·25
Nephritis		0·16	0·14	0·29	0·17	0·09
Total		9·03	9·05	9·93	9·51	7·86
Total hypertensive		1·20	1·22	1·17	1·25	1·10

*(a) Without reference to hypertension on the death certificate.
†(b) Hypertension referred to on the death certificate.

TABLE 20.—*Death Rate from Coronary Thrombosis by Age**

Age in Years	No. of Deaths	Death Rate per 1,000				
		Non-smokers	Current Cigarette Smokers Smoking Daily			All Cigarette Smokers, Ex and Current
			1–14	15–24	25+	
35–44	36	0·11	0·41	0·49	1·50	0·61
45–54	149	1·12	1·95	3·43	2·73	2·61
55–64	319	4·01	6·41	7·03	8·41	7·20
65–74	309	10·83	16·44	13·04	17·59	14·69
75–84	314	21·20	21·22	15·34	17·20	19·15
85+	78	32·35	31·06	36·54	—†	35·05
All ages	1,267	3·31	4·36	4·28	4·97	4·30

*Includes all deaths attributed to coronary thrombosis, except those for which hypertension was mentioned as a contributory cause (V).
†Very small total number of man years at risk (27)—no deaths due to coronary thrombosis.

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Source: https://www.industrydocuments.ucsf.edu/docs/jslk0000

An analysis was made by Schor (*86*) of 181 adult males who died from coronary heart disease generally less than 2 years after receiving a periodic health examination. The results of this study and those of Doll and Hill suggest that sudden death from previously undetected coronary heart disease frequently occurs among cigarette smokers. If this is true, it may, in part, account for the small differentials in the prevalence of coronary heart disease between smokers and nonsmokers observed in some morbidity prevalence surveys. As will be described in the following section, longitudinal, prospective morbidity studies also show that smokers are more likely to die from sudden attacks of coronary heart disease.

Coronary Heart Disease Morbidity*

In chapter 11 of the 1964 Surgeon General's Report, several prospective studies on the incidence of coronary heart disease (*24, 31, 78, 88*) established that smokers were subject to higher rates than nonsmokers. The relationship was reported to be more marked under 50 years of age than among older persons and appeared to be associated with myocardial infarction but not with angina pectoris. Since the 1964 report, recent findings from large-scale, on-going prospective studies have been reported, providing additional insight on the interaction between smoking and other important coronary heart disease risk factors. Current findings are summarized in the following pages including tables 7 to 13. Whenever possible, data are shown separately for findings related to angina pectoris and those pertaining to myocardial infarction, including sudden death attributed to coronary heart disease. Higgins (*50*) has drawn attention to the fact that "many factors may influence or be affected by smoking habits, and obscure those differences between smokers and nonsmokers which are directly related to the use of tobacco." In her review of the literature, Higgins identified differences between smokers and nonsmokers in genetically determined qualities (*23*), in physique (*77, 93*), in personality (*37, 47, 48, 65, 68, 69*), and in social, cultural, religious, and economic characteristics (*40, 49, 68, 84*).

*Also may include mortality data in this presentation.

(86) Schor, S. S., Elsom, K. A., Elsom, K. O., Dunn, J. P. An evaluation of the periodic health examination: A study of factors discriminating between survival and death from coronary heart disease. Annals of Internal Medicine (Philadelphia) 61(6): 1006–1014, December 1964.

(24) Dawber, T. R., Kannel, W. B., Revotskie, N., Stokes, J., Kagan, A., Gordon, T. Some factors associated with the development of coronary heart disease. Six years' followup experience in the Framingham study. American Journal of Public Health and the Nation's Health (New York) 49(10): 1349–1356, October 1959.

(31) Doyle, J. T., Heslin, A. S., Hillebor, H. E., Fornfel, P. F. Early diagnosis of ischemic heart disease. The New England Journal of Medicine (Boston) 261(22): 1096–1101, November 1959.

(78) Paul, O., Lepper, M. H., Phelan, W. H., Dupertuis, G. W., MacMillan, A., McKean, H., Park, H. A longitudinal study of coronary heart disease. Circulation; Journal of the American Heart Association (New York) 28: 20–31, July 1963.

(88) Spain, D. M., Nathan, D. J. Smoking habits and coronary atherosclerotic heart disease. Journal of the American Medical Association (Chicago) 177(10): 683–688, September 1961.

(50) Higgins, M., Kjelsberg, M. Characteristics of smokers and nonsmokers in Tecumseh, Mich. II. The distribution of selected physical measurements and physiological variables and the prevalence of certain diseases in smokers and nonsmokers. (In press.) American Journal of Epidemiology (Baltimore): 1967. 27 pp.

(23) Cohen, B. H., Thomas, C. B. Comparison of smokers and nonsmokers. II. The distribution of ABO and Rh (D) blood groups. Bulletin of the Johns Hopkins Hospital (Baltimore) 110: 1–7, January 1962.

(77) Parnell, R. W. Smoking and cancer. Lancet (London) 1: 993, 1951.

(93) Thomas, C. B. Characteristics of smokers compared with nonsmokers in a population of healthy young adults, including observations on family history, blood pressure, heart rate, body weight, cholesterol, and certain psychologic traits. Annals of Internal Medicine (Philadelphia) 53: 697–718, October 1960.

(37) Eysenck, H. J., Tarrant, M., Woolf, M., England, L. Smoking and personality. British Medical Journal (London) 1(5181): 1456–1460, May 14, 1960.

(48) Heath, C. W. Differences between smokers and nonsmokers. American Medical Association Archives of Internal Medicine (Chicago) 101: 377–388, February 1958.

(65) Lilienfeld, A. M. Emotional and other selected characteristics of cigarette smokers and nonsmokers as related to epidemiological studies of lung cancer and other diseases. Journal of the National Cancer Institute (Washington) 22(2): 259–282, 1959.

(68) McArthur, C., Waldron, E., Dickinson, J. The psychology of smoking. Journal of Abnormal Psychology (Washington) 56: 267–275, 1958.

(69) Matarazzo, J. D., Saslow, G. Psychological and related characteristics of smokers and nonsmokers. Psychological Bulletin (Washington) 57(6): 493–513, November 1960.

(36) Haenszel, W., Shimkin, M. B., Miller, H. P. Tobacco smoking patterns in the United States. Washington. U.S. Department of Health, Education, and Welfare, Public Health monograph No. 45. Public Health Service publication No. 463. 1956. 111 pp.

(49) Higgins, M., Kjelsberg, M., Metzner, H. Characteristics of smokers and nonsmokers in Tecumseh, Mich. I. The distribution of smoking habits in persons and families and their relationship to social characteristics (In press). American Journal of Epidemiology (Baltimore): 1967.

(84) Salber, E. J., MacMahon, B. Cigarette smoking among high school students related to social class and parental smoking habits. American Journal of Public Health and the Nation's Health (New York) 51(12): 1780–1789, December 1961.

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Sudden Deaths. This paragraph implies that sudden death occur more frequently among smokers, Schor et al. (86) specified one group of sudden deaths, i.e. those who die from coronary disease undetected. The incidence of sudden deaths of smokers compared to nonsmokers cannot be derived from the article. A portion of the Discussion is as follows:

> The person who dies from coronary heart disease which has escaped detection constitutes a special problem. In our population 42% were in this category. Our findings show that, by our present techniques, such a person more closely resembled his alive counterpart without evidence of heart disease than he did the person who died with the diagnosis of the disease. Furthermore, this person died somewhat sooner after his last examination than did the man in whom the disease had been identified. The lethal process can, therefore, be presumed to have been advanced at the time of examination. Clearly, new or improved methods will be required to distinguish this man from normal persons. Recent studies (2) suggest that differences may reside in social, personality, or other factors that are not now tested in the usual periodic health examination. The one finding that, in our study, distinguished this man from his living counterpart, was heavy cigarette smoking. Whether this, as such, is an important factor or simply a reflection of some other factor we are not in a position to say.

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Age

The effect of age on the incidence of coronary heart disease with regard to cigarette smoking is shown in table 7 based on recent data from the Framingham Study as yet unpublished.

TABLE 7.—*Incidence rates and morbidity ratios for coronary heart disease by age and smoking status of men 12-year experience, Framingham, Mass.*

Age	Incidence rates per 1,000		Excess rates per 1,000	Morbidity ratio	
	Non-smokers	Smokers	Smokers minus non-smokers	Non-smokers	Smokers
35 to 44	1.4	4.1	2.7	1.0	2.9
45 to 54	4.6	11.1	6.5	1.0	2.4
55 to 64	16.2	25.4	9.2	1.0	1.6

Source: U.S. Public Health Service, Framingham Study (95). (Updated 1967)

When the incidence rate of coronary heart disease among male nonsmokers between 35–44 years of age is compared with that among older nonsmokers, the rate is seen to triple every 10 years. This marked increase in incidence among nonsmokers reflects the effect of other important risk factors and perhaps accounts for the decrease in morbidity ratio as age advances. The independent effect of smoking on the incidence of coronary heart disease is believed to be more appropriately represented by the excess morbidity rates, which increase from 2.7 per 1,000 smokers in the age group 35–44 to 9.2 per 1,000 smokers 55–64 years of age.

High Blood Pressure

Although the inhalation of cigarette smoke is frequently accompanied by acute transient elevations in blood pressure, habitual smokers tend to have lower blood pressures than do nonsmokers (*48*). But, given the presence of high blood pressure in an individual, smoking acts as an additional risk factor for the development of coronary heart disease (*17, 28, 29, 50, 53, 55, 56, 96*). Both the independent and the combined effect of cigarette smoking is clearly shown in table 8 derived from the experience of the Framingham and Albany studies (*50*).

TABLE 8.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of systolic blood pressure*

Systolic blood pressure	Nonsmokers of cigarettes	Cigarette smokers
Under 130 mm. Hg	1.0	2.1
130 mm. Hg and over	1.8	3.8

Source: 10-year Framingham and 6-year Albany experience (50).

High Serum Cholesterol

It is not now conclusively known if cigarette smoking by itself can cause increases in serum cholesterol. Dietary influences as well as endogenous production and elimination of cholesterol must be evaluated in greater detail with simultaneous analysis of the roles of other risk factors, including smoking. One study of a small population of twins in Sweden, as reported by Lundman (*67*), suggests that smoking monozygotic twins tend to have lower cholesterol levels than their nonsmoking control twins, although the differences are not statistically significant. Other studies suggest that smokers generally have higher serum cholesterol than nonsmokers (*13, 67, 88*). However, given the presence of high serum cholesterol, smoking increases the risk of coronary heart disease (*95, 96*).

The independent and synergistic effect of cigarette smoking is demonstrated by the data in table 9 derived from the combined experience of the Framingham and Albany studies (*50*).

TABLE 9.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of serum cholesterol*

Serum cholesterol level	Nonsmokers of cigarettes	Cigarette smokers
Low[1]	1.0	1.8
High[1]	2.0	4.5

[1] "Low" is below median, "High" is above median value of serum cholesterol.
Source: 10-year Framingham and 6-year Albany experience (50).

(96) U.S. PUBLIC HEALTH SERVICE. The Framingham Heart Study. Habits and Coronary Heart Disease. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service, Publication No. 1515, 1966.

(28) DOYLE, J. T. Etiology of coronary disease: Risk factors influencing coronary disease. Modern Concepts of Cardiovascular Disease (Baltimore) 35: 81–86, April 1966.

(29) DOYLE, J. T., DAWBER, T. R., KANNEL, W. B., HESLIN, A. S., KAHN, H. A. Cigarette smoking and coronary heart disease. Combined experience of the Albany and Framingham studies. New England Journal of Medicine (Boston) 266(16): 796–801, Apr. 19, 1962.

(50) DOYLE, J. T., DAWBER, T. R., KANNEL, W. B., KINCH, S. H., KAHN, H. A. The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, N.Y., and Framingham, Mass., studies. Journal of the American Medical Association (Chicago) 190(10): 886–890, Dec. 7, 1964.

(53) KANNEL, W. B. Cigarette smoking and coronary heart disease (editorial). Annals of Internal Medicine (Philadelphia) 60(6): 1103–1106, June 1964.

(55) KANNEL, W. B., DAWBER, T. R., MCNAMARA, P. M. Detection of the coronary-prone adult: The Framingham study. Journal of the Iowa Medical Society (Des Moines) 55(1): 26–34, January 1965.

(95) TRUETT, J., CORNFIELD, J., KANNEL, W. A multivariate analysis of the risk of coronary heart disease in Framingham. [Unpublished.] 26 pp.

(67) LUNDMAN, T. Smoking in relation to coronary heart disease and lung function in twins. A co-twin control study. Acta Medica Scandinavica (Stockholm) 180 (Supplement 455): 1–75, 1966.

(13) BENSON, H., COSTAS, R., JR., GARCIA-PALMIERI, M. R., FELDREICH, M., AZCAL, R., BLANTON, J. H., COLON, A. A. Coronary heart disease risk factors: A comparison of two Puerto Rican populations. American Journal of Public Health and the Nation's Health (New York) 56(7): 1037–1060, July 1966.

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Smoking and hypercholesterolemia. This subject has been alluded to in the commentary of 1964 document, page 354a. There are several studies indicating that there is no relationship between smoking and cholesterol levels (page 207-210).

The cited article (13) Benson et al. does not show that smokers generally have higher serum cholesterol levels than nonsmokers. The Results quoted from the article are as follows:

> The mean serum cholesterol was also higher in urban men in both age groups (Table 1). Twenty-one per cent of the younger urban men and 12 per cent of the older urban men had serum cholesterol levels of greater than 260 mg per cent in contrast to 11 per cent of the younger and none of the older rural males.
>
> Urban men smoked less than their rural cohorts. The percentage of cigarette smokers in urban men was less in both age groups, but was statistically significant only in the younger age group (Table 1). However, there was a higher percentage of "heavy" (greater than one pack per day) cigarette smokers in the urban men in each age group (Table 1).

Table 1—Comparison of urban and rural males

	Age Group	Number of Subjects Urban	Number of Subjects Rural	Urban	Rural	p
Mean systolic and diastolic blood pressure (mmHg)	45-54	33	28	139/87	121/76	<0.001*
	55-64	17	16	154/90	127/76	<0.001*
Relative weight	45-54	33	28	107	98	<0.02†
	55-64	17	16	100	95	<0.03†
Mean serum cholesterol (mg/100cc)	45-54	33	28	231	211	<0.02†
	55-64	17	16	220	199	<0.10
Per cent cigarette smokers	45-54	33	28	42	86	<0.001†
	55-64	17	16	29	56	<0.12
Per cent "heavy" (greater than 1 pack/day) cigarette smokers	45-54	14‡	23‡	64	35	—
	55-64	5‡	9‡	80	55	—
Per cent "abnormal" electrocardiograms	45-54	33	28	15	7	<0.42
	55-64	16	16	6	12	<0.55
Mean hematocrit (%)	45-54	33	28	45	44	<0.42
	55-64	17	16	43	45	<0.11

* Statistically significant for both systolic and diastolic.
† Statistically significant.
‡ Total number who are present smokers.

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Pulmonary Function

The acute effects of cigarette smoking upon pulmonary function are expressed mainly through increase in airway resistance. The differences in pulmonary function between smokers and nonsmokers appear to be greater than can be accounted for by acute effects from a recently smoked cigarette (*30, 91*). The relationship of coronary heart disease to lowered pulmonary function as reflected by low vital capacity and cigarette smoking is observed in the data published by the National Institutes of Health based on the 12-year experience in Framingham (*36*). Morbidity ratios derived from this publication are shown in table 10.

TABLE 10.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of vital capacity*

Vital capacity	Nonsmokers of cigarettes	Cigarette smokers
Under 3 liters	1.0	1.7
3 liters or more	1.7	2.4

Source: The Framingham heart study. (36).

Here again, the independent and combined effects of cigarette smoking are observed.

Physical Inactivity

A physically inactive or sedentary individual seems to run a higher risk of developing coronary heart disease (*33, 40, 41, 76*). Spain (*88*) reported that, in his prospective study of 3,000 men "* * * the relationship of occupational physical activity to smoking habits revealed that one of six sedentary workers were heavy smokers and one of five strenuous workers were heavy smokers." Weinblatt, in reporting the experience of the Health Insurance Plan of Greater New York (*100*) also found that a higher proportion (41.9 versus 33.0 percent) of cigarette smokers were classified in the "most active" physical activity category.

The independent and the combined effects between cigarette smoking and physical activity are shown in table 11. The morbidity ratios for myocardial infarctions are derived from published data.

TABLE 11.—*Age-adjusted morbidity ratios for myocardial infarctions among smokers and nonsmokers according to physical activity level*

Physical activity	Nonsmokers of cigarettes	Cigarette smokers
Most active	1.0	2.6
Least active	2.4	3.4

Source: Weinblatt, E. (100).

Socioenvironmental Stress

Since 1955, research on socioenvironmental stress in relation to coronary heart disease has increased greatly (*83, 92*). Among the factors studied that indicate a strong association with coronary heart disease incidence and prevalence is sociocultural mobility, that is, moving from one social setting to another. The interaction of this factor and cigarette smoking has been reported by Syme (*89, 91*) in both an urban and rural setting. Apparently in both areas cigarette smokers were more culturally mobile than nonsmokers. The independent effect of cigarette smoking on the incidence of coronary heart disease is shown in the morbidity ratios in table 12 derived from the North Dakota study (*91*).

TABLE 12.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to sociocultural mobility status*

Sociocultural status	Never smoked cigarettes	Current and former cigarette smokers
Stable	1.0	1.5
Highly mobile	2.3	3.2

Source: North Dakota study. (91)

(91) SYME, S. L., HYMAN, M. M., ENTERLINE, P. E. Some social and cultural factors associated with the occurrence of coronary heart disease. Journal of Chronic Diseases (St. Louis) 17: 277-289, 1964.

(33) FOX, S. M., III, SELNNER, J. S. Physical activity and cardiovascular health. American Journal of Cardiology (New York) 14(6): 731-746, December 1964.

(40) FRANK, C. W., WEINBLATT, E., SHAPIRO, S., SAGER, R. V. Myocardial infarcation in men. Role of physical activity and smoking in incidence and mortality. Journal of the American Medical Association (Chicago) 198(12): 1241-1245, Dec. 19, 1966.

(41) FRANK, C. W., WEINBLATT, E., SHAPIRO, S., SAGER, R. V. Physical inactivity as a lethal factor in myocardial infarction among men. Circulation; Journal of the American Heart Association (New York) 34: 1022-1033, December 1966.

(76) PAFFENBARGER, R. S., JR., WOLF, P. A., NOTKIN, J., THORNE, M. C. Chronic disease in former college students. I. Early precursors of fatal coronary heart disease. American Journal of Epidemiology (Baltimore) 83(2): 314-328, 1966.

(100) WEINBLATT, E. Personal communication. Health Insurance Plan of Greater New York, Apr. 17, 1967.

(83) RUSSEK, H. I. Stress, tobacco, and coronary disease in North American professional groups. Survey of 12,000 men in 14 occupational groups. Journal of the American Medical Association (Chicago) 192(3): 189-194, April 19, 1965.

(92) SYME, S. L., BRESLOW, L. G., editors. Social stress and cardiovascular disease. Proceedings of the National Workshop Conference on Socio-environmental Stress and Cardiovascular Disease, Phoenix, Ariz., Feb. 14 to 16, 1966. The Milbank Memorial Fund Quarterly (New York) 45 (No. 2, pt. 2): 1-192, April 1967.

(89) SYME, S. L., BORHANI, N. O., BUECHLEY, R. W. Cultural mobility and coronary heart disease in an urban area. American Journal of Epidemiology (Baltimore) 82(3): 334-346, November 1965.

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Pulmonary Function in Smokers. The cited articles (50, 91, 96) do not relate to a comparison of pulmonary function between smokers and nonsmokers. However, this topic was investigated by (21) Chevalier et al. in an earlier publication (1963), and by (61) Krumholz et al., 1964. These articles are quoted in the 1967 document in relation to exercise (page 367). These investigators did not find any significant difference in vital capacity or airway resistance between smokers and nonsmokers. The Results from Chevalier et al (J Appl Physiol 18: 357-360, 1963) and Krumholz et al. (Ann Intern Med 60: 603-610, 1964) are as follows:

TABLE 2. *Pulmonary characteristics of subjects*

	Smokers	Nonsmokers
Vital capacity, ml	5,009 ± 627	3,384 ± 4[illegible]
Total lung capacity, ml	6,930 ± 838	7,185 ± [illegible]
RV/TLC, %	26.1 ± 4.9	26.2 ± 5.4
Airway resistance, cm H_2O liter sec	1.82 ± .61	1.69 ± 5[illegible]
1-Sec timed vital capacity, % of total	84.6 ± 8	89.5 ± 6
Max. expiratory flow rate, liters/min	596 ± 84	600 ± 6[illegible]
Max. breathing capacity, % of predicted normal	101.7 ± 18.3	98.9 ± 8[illegible]

Values are expressed as the mean ±1 SD. There is no significant difference ($P > .05$) between mean values for the two groups.

Subjects	Inspiratory* Capacity	Inspiratory Reserve Volume	Expiratory Reserve Volume	Tidal Volume	Vital Capacity	Functional Residual Capacity	Residual Volume	Total Lung Capacity	Residual Volume/ Total Lung Capacity	Maximal Voluntary Ventilation	Maximum Expiratory Flow Rate	Airway Resistance
	ml	*ml*	*ml*	*ml*	*ml*	*ml*	*ml*	*ml*	%	*liter/min*	*liter/min*	*cm H₂O/ liter/sec*
Smokers												
1	3,170	2,400	1,420	770	4,590	2,600	1,180	5,770	20	147	420	1.27
2	2,760	2,160	2,430	600	5,190	4,700	2,270	7,460	30	142	570	.62
3	3,160	2,180	2,050	980	5,220	4,400	2,350	7,570	31	168	680	1.09
4	2,570	1,920	2,040	650	4,610	3,900	1,860	6,470	29	141	550	1.21
5	3,220	2,470	2,170	750	5,380	3,600	1,430	6,810	21	168	650	.97
6	2,940	2,110	2,580	830	5,520	4,600	2,020	7,540	26	184	660	1.04
7	2,180	1,490	2,600	690	4,790	3,400	800	5,590	14	142	520	.85
8	3,800	2,710	890	1,090	4,690	1,800	910	5,600	16	173	550	.83
9	3,590	2,540	1,920	1,050	5,540	3,500	1,580	7,120	22	206	710	1.03
Mean:	3,040±500†	2,220±370	2,010±560	820±80	5,060±380	3,610±950	1,600±570	6,650±690	23±6	163±24	590±90	.98±.19
Nonsmokers												
1	3,710	2,830	2,780	880	6,490	5,200	2,420	8,910	—	154	570	.90
2	3,650	1,950	1,400	1,700	5,050	3,200	1,800	6,850	26	203	610	1.02
3	3,500	2,540	1,560	960	5,050	3,500	1,940	6,990	28	177	640	.71
4	3,370	2,820	3,400	550	6,780	6,700	3,300	10,080	33	169	640	1.13
5	3,630	3,140	2,550	490	6,190	4,100	1,550	7,740	20	146	600	.83
6	3,180	2,050	1,910	1,130	5,100	3,800	1,890	6,990	27	161	560	.74
7	4,220	3,300	2,160	920	6,380	3,800	1,640	8,020	20	166	480	1.03
8	4,030	3,400	2,010	630	6,050	3,600	1,590	7,640	21	161	640	.53
9	3,260	1,750	1,120	1,500	4,370	4,400	3,280	7,650	43	123	510	.82
Mean:	3,610±350	2,640±610	2,100±720	970±390	5,720±830	4,260±1,090	2,160±690	7,870±1,060	25±13	162±22	580±60	.86±.19
P	>.05	<.10	>.80	>.50	<.05	>.80	>.10	<.05	>.50	>.50	>.30	>.20

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Personality Type

Various investigators have long suspected a possible pathogenetic role of the central nervous system in coronary heart disease (*35*). In a series of reports, Rosenman (*81, 82*) and Jenkins (*51*) have described a personality pattern or overt emotional complex which, while associated with other known risk factors, appears to predict coronary heart disease more effectively than do other risk factors. This emotional complex, "which they have termed Behavior Pattern Type A, is composed of an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency." Recent unpublished data based upon prospective observation of more than 3,000 men for a 4½-year period (*51*) discloses that smokers have a higher percentage (54 versus 47 percent) of type A persons among them. Moreover, the incidence of coronary heart disease is shown to be related independently to both smoking status and personality type. Morbidity ratios, derived from the incidence data, are shown in table 13 which clearly demonstrates the independent effects of cigarette smoking and its interaction with personality characteristics.

TABLE 13.—*Morbidity ratios of cigarette smokers as compared to nonsmokers by personality type*

Personality type	Nonsmokers of cigarettes	Cigarette smokers
Behavior type B	1.0	2.0
Behavior type A	2.5	4.4

SOURCE: Unpublished data from Western Collaborative Group Study, San Francisco, Calif. (*51*).

Multiple-Risk Factors

The method of analysis traditionally employed by epidemiologists, that of the comparison of rates for multiple cross-classifications of the data, generally requires a large study population at relatively high incidence of significant events. Since coronary heart disease incidence rates are low and study populations are necessarily small because of practical and practicable limitations, definitive analysis of the independence and interaction between risk factors have generally been restricted to two factors at a time. Truett (*95*) applied a multiple logistic function proposed by Cornfield to investigate the independent effect on the incidence of coronary heart disease of seven risk factors: Age, serum cholesterol, systolic blood pressure, relative weight, hemoglobin, cigarettes per day, and ECG abnormalities. The method was used in the analysis of data compiled in the Framingham study during a 12-year period. A discriminant function coefficient was computed for each risk factor. These coefficients represent the relative importance of each factor with respect to the other six factors in the development of coronary heart disease. While theoretical considerations underlying the logistic risk function are not fully satisfied by the actual data, the approximation given by the function to observed rates is very good.

Consequently, Truett and Cornfield believe that the present computations permit the conclusion that "the most important risk factors, aside from age itself, are cholesterol, cigarette smoking, ECG abnormality, and blood pressure" (*95*).

(35) EPSTEIN, F. H. The epidemiology of coronary heart disease: A review. Journal of Chronic Diseases (St. Louis) 18(5): 735–771, August 19[illegible].

(81) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, D., STRAUS, R., WURM, M., KOSITCHEK, R. The prediction of immunity to coronary heart disease. Journal of the American Medical Association (Chicago) 194(11): 1[illegible]-1102, Dec. 12, 1965.

(82) ROSENMAN, R. H., FRIEDMAN, M., STRAUS, R., WURM, M., KOSITCHEK, R., HAHN, W., WERTHESSEN, N. T. A predictive study of coronary heart disease. Journal of the American Medical Association (Chicago) 189(1): 15–22, July 6, 1964.

(51) JENKINS, C. D. Personal communication. The University of North Carolina, Chapel Hill, Apr. 10, 1967.

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Manifestation of Coronary Heart Disease

Coronary heart disease is essentially comprised of three major manifestations or subcategories:

1. Fatal myocardial infarctions, including sudden deaths attributed to coronary heart disease;
2. Nonfatal myocardial infarction; and
3. Angina pectoris.

Generally, investigators in their analysis of the relationship of risk factors to the incidence of coronary heart disease have not subdivided the observed coronary events into the three major subcategories primarily because the paucity of events in each category did not permit definitive conclusions on any differences observed. However, the pooling of data from some of the larger prospective studies holds promise of a more complete analysis of the independent and synergistic effects of each risk factor on each of the subcategories of coronary disease. Findings from these analyses might provide some insights into the underlying pathophysiological mechanisms through which a risk factor operates. The pooled data from the Albany and Framingham studies and data from the HIP study include the observed associations of cigarette smoking with each of the three major manifestations. Morbidity ratios have been derived from these studies and are presented in table 14.

TABLE 14.—*Age-adjusted morbidity ratios for subcategories of coronary heart disease among smokers and nonsmokers*

Disease category	Framingham-Albany		Health insurance plan	
	Non-smokers of cigarettes	Cigarette smokers	Non-smokers of cigarettes	Cigarette smokers
Fatal myocardial infarction	1.0	2.4	1.0	2.1
Non-fatal myocardial infarction	1.0	2.3	1.0	1.8
Angina pectoris	1.0	1.1	1.0	1.7

SOURCE: Second Report of the Combined Experience from Albany and Framingham Studies (32). Unpublished Data from Health Insurance Plan Study (36).

The association of cigarette smoking to angina pectoris is not a consistent one. A clear-cut association was found in the Health Insurance Plan Study (ratio of 1.7); a similar association is also found in unpublished data from Framingham considered separately. However, no association between cigarette smoking and the incidence of angina pectoris was found in the Albany experience. Cederlof (*19*), in his analysis of prevalence data on angina pectoris obtained by questionnaire, found no statistically significant difference in prevalence rates between 453 monozygotic twin pairs with dissimilar smoking habits. In a larger study of about 9,000 persons from the twin register where genetic factors were uncontrolled, Cederlof (*12, 20*) did find a significantly higher prevalence of angina pectoris among smokers than nonsmokers, particularly in men (ratio of 1.6) (*67*).

Friedman (*42*) and Epstein (*36*) have clearly described the inherent biases in prevalence studies which may lead to findings of risk gradients that are different from those obtained in prospective incidence studies. One of these limitations is that fatal cases are underrepresented in a prevalence survey. Thus, since it appears that cigarette smoking is more closely related to the incidence of fatal myocardial infarctions than to other forms of coronary heart disease, it is expected that morbidity ratios derived from prevalence surveys would be lower than those computed from incidence data. With these restrictions in mind, Russek (*83*) in a survey of 12,000 men in 14 occupational groups found that the morbidity ratio of coronary heart disease prevalence among cigarette smokers was as high as 1.8. In contrast, in a study of 77 identical and 89 fraternal twins in Sweden, comparing smokers with their respective nonsmoking twins, Lundman (*67*) reported no excess prevalence of overt or silent coronary heart disease. However, the prevalence of these conditions, as Lundman concluded, "was too low to permit of definitive conclusions."

(19) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Morbidity among monozygotic twins. Archives of Environmental Health (Chicago) 10(2): 340–350. February 1965.

(20) CEDERLOF, R. FRIBERG, L., JONSSON, E., KAIJ, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. Archives of Environmental Health (Chicago) 13(6): 725–737, December 1966.

(42) FRIEDMAN, G. D. Cigarette smoking and geographic variation in coronary heart disease mortality in the United States. Presented at Conference on Epidemiology of Cardiovascular Disease, American Heart Association, Chicago, Illinois, Feb. 3, 1967. [Unpublished.] 23 pp.

(36) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine (London) 60: 56–60, January 1967.

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Twin Registry. This paragraph omits the significance of investigation of twins. The two sentences are correct but the significance is not discussed for the benefit of the general reader. A portion of the Conclusions of (20) Cederlof et al. is as follows:

/ The results obtained from group A, including only *one* twin from each pair, regardless of smoking habits, are, from the constitutional point of view, as heterogeneous as "normal material." These results reveal a marked association between smoking and symptoms. Thus, "angina pectoris" occurred throughout, to a greater extent among smokers than among nonsmokers, as did the different degrees of bronchial symptoms.

In regard to respiratory symptoms, the findings are fully in accord with previously reported experience.[1]

The question of hypermorbidity among smokers in regard to coronary disease has not received the same unanimous answer in published investigations. Extensive prospective studies of mortality from coronary disease, however, point unanimously to a connection with smoking.[17-21] As for morbidity in angina pectoris among smokers, an early report from the Framingham study[22] showed data that suggested an increased risk among men who smoked over 20 cigarettes per day. Later experience gained from the combined Albany and Framingham studies[20] have not verified an increased incidence of angina pectoris among smokers. A report published by the Health Insurance Plan of Greater New York on the incidence and prognosis of coronary disease found a clear hypermorbidity in angina pectoris among male smokers but not among women.[21]

Our material revealed a clear hypermorbidity in "angina pectoris" among male smokers in the series where genetic factors were uncontrolled (group A). A corresponding hypermorbidity could not be ascertained, however, when intrapair comparisons were made between smoker and nonsmoker in discordant twin groups. This difference in morbidity between the groups cannot be accounted for by differences in degree of exposure to tobacco. This is shown by the factual data concerning tobacco consumption and by the fact that the same degree of hypermorbidity was found in smokers' respiratory symptoms. Therefore, it seems highly probable that factors other than exposure to tobacco were of decisive importance. One such possible factor could lie in the fact that the smokers in group A tended more than those in the B groups to be town dwellers. However, investigations carried out to date make such an interpretation highly improbable.[23]

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Cardiovascular Response to Smoking and/or Nicotine

As noted in the Surgeon General's 1964 Report, nicotine has definite physiologic effects on the cardiovascular system of experimental animals and of man. These include increases in heart rate, systemic arterial pressure, cardiac output, stroke volume, and velocity of myocardial contraction, all resulting in an increased myocardial tissue oxygen demand (*16*). Coronary blood flow studies will be reported in the next section under a separate subheading. These effects parallel those observed with catecholamines (epinephrine and norepinephrine). The effects can be blocked by the injection of tetraethylammonium chloride and markedly reduced by adrenalectomy (*22*). Nicotine has been repeatedly shown to release endogenous catecholamines (*57, 58, 59, 60, 102*). However, the mechanism by which nicotine affects the cardiovascular system is more complex than the release of catecholamines from the adrenal medulla. Direct and indirect (via the carotid body and other chemoreceptors) stimulation of the vasomotor center, stimulation of sympathetic ganglia, release of norepinephrine from local stores, and release of antidiuretic hormone are included among other postulated mechanisms of action involved in nicotine's effect on the cardiovascular system (*16, 63, 85*).

Coronary Blood Flow in Normal Subjects

The action of smoking and/or nicotine on the coronary blood flow of normal human subjects has not yet been definitively established, but apparently normal subjects can increase their coronary blood flows sufficiently to maintain a compensatory blood supply to the myocardium despite the increased myocardial tissue demand for oxygen caused by cigarette smoking. Earlier findings of increased coronary blood flow in normal men, in response to cigarette smoking (*11*), were not reproduced in a more recent study (*76*). In this latter study, although a trend towards a slight increase in coronary blood flow was observed in the particular normal persons studied, it was not significant.

Direct injection of nicotine into the left coronary artery of dogs under conditions of constant flow rate resulted in increased coronary vascular resistance (*38, 64*). This response could be reduced by vagal nerve stimulation or prior administration of acetylcholine; an immediate increase in cardiac contractile force was also observed that could be similarly reduced. It was concluded that these responses to nicotine resulted from sympathetic nervous system activity or from the release of catecholamines by myocardial chromaffin tissue (*64*).

Blood from the smoke-exposed lung tissue of dogs, directly perfused into the coronary artery, failed to increase coronary resistance (*33*). This effect was thought to be secondary to that of histamine, known to act as a coronary vasodilator, which apparently is released from the lung tissue of dogs during their exposure to smoke (*5*).

When blood from the smoke-exposed lung was perfused through the systemic circulation of dogs while the coronaries were being perfused with non-smoke-exposed blood, the typical release of catecholamines occurred with many of the usual effects on cardiovascular parameters except that the coronary vascular resistance increased under these experimental conditions, apparently due to the increased activity of the sympathetic nervous system (*38*).

Since it is well known that exposing dogs to cigarette smoke without isolating and separately perfusing the coronary circulation normally results in an increase of the coronary blood flow (*38*), the manipulation of experimental conditions as described suggests that there is a masking effect by the catecholamines on nicotine's direct action on the coronary circulation (*38*).

These studies may relate, by analogy, to humans and indicate that smoking, in "normal" individuals, may produce at least two actions that can affect coronary blood flow: (1) a decrease in coronary blood flow by a possible direct action of nicotine on the coronary circulation (demonstrated in dogs), and (2) an increase in coronary blood flow as the usual resultant of varying responses to the intermediating action of catecholamines and other physiologic processes (demonstrated in both animals and humans).

(16) Bing, R. J., Cohen, A., Buechner, C. Tobacco alkaloids and circulation. *In:* Tobacco Alkaloids and Related Compounds. Proceedings of the 1st International Symposium held at the Wenner-Gren Center, Stockholm, February 1964: 1965. Pp. 211–231.

(22) Chiang, T. S., Leaders, F. E. Cardiostimulatory responses to vagal stimulation, nicotine, and tyramine. American Journal of Physiology (Washington) 211(6): 1413–1416, December 1966.

(57) Kershbaum, A., Bellet, S. Cigarette smoking and blood lipids. Journal of the American Medical Association (Chicago) 197(1): 52–56, Jan. 4, 1966.

(58) Kershbaum, A., Bellet, S. Smoking as a factor in atherosclerosis. Geriatrics (Minneapolis) 21(12): 155–170, December 1966.

(59) Kershbaum, A., Bellet, S., Jimenez, J., Peinado, L. J. Differences in effects of cigar and cigarette smoking on free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association (Chicago) 195(13): 1095–1098, Mar. 28, 1966.

(60) Krumholz, R. A. Pulmonary membrane diffusing capacity and pulmonary capillary blood volume: An appraisal of their clinical usefulness. American Review of Respiratory Diseases (Baltimore) 94(2): 195–200, August 1966.

(102) Westfall, T. C., Cipollone, P. B., Edmundowicz, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine (New York) 123: 174–179, 1966.

(63) Larson, R. K., Fukuda, P., Murray, J. F. Systemic and pulmonary vascular effects of nicotine in anesthetized dogs. American Review of Respiratory Diseases (Baltimore) 91(4): 550–564, April 1965.

(85) Samanek, M., Aviado, D. M. Cardiopulmonary effects of tobacco and related substances. III. Pulmonary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health (Chicago) 12(6): 727–732, June 1966.

(11) Barreiro, L. M., Jr., Ehmke, D., Gonzalez, F., Castellanos, F. A., Siegel, A., Pino, R. J. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation; Journal of the American Heart Association (New York) 15: 251–257, 1957.

(38) Folle, L. E., Samanek, M., Aviado, D. M. Cardiopulmonary effects of tobacco and related substances. II. Coronary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health (Chicago) 12(6): 712–716, June 1966.

(64) Leaders, F. E., Long, J. P. Action of nicotine on coronary vascular resistance in dogs. American Journal of Physiology (Washington) 208(5): 621–625, October 1965.

(5) Aviado, D. M., Samanek, M., Folle, L. E. Cardiopulmonary effects of tobacco and related substances. I. The release of histamine during inhalation of cigarette smoke and anoxemia in the heart-lung and intact preparation. Archives of Environmental Health (Chicago) 12(6): 703–724, June 1966.

(1) Ashby, P., Daley, A. M., Millar, J. H. D. Smoking and platelet stickiness. Lancet (London) 2: 158–159, July 21, 1965.

(2) Astrup, P. An abnormality in the oxygen-dissociation curve of blood in patients with Buerger's disease and patients with pulmonary arteriosclerosis. Lancet (London) 2: 1152–1154, Nov. 26, 1966.

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Cigarette smoke on coronary vascular resistance. The interpretation of the perfusion experiments by (8) Aviado et al and (38) Folle et al is not complete. The authors mention a second explanation in that the amount of nicotine absorbed in the lungs is not sufficient to influence the coronary vessels. The quotation from Folle et al is as follows:

> The perfused coronary artery behaved in the following manner: no immediate change when blood exposed to cigarette smoke was perfused into the coronary artery but an increase in coronary vascular resistance when nicotine was injected directly into the vessel. There are two possible explanations for this discrepancy: (*a*) that the amount of nicotine absorbed from the left lower lobe was less than the 1μg/kg injected directly into the perfused artery; or (*b*) that blood exposed to cigarette smoke did not act in the same manner as pure nicotine. In regard to the latter possibility, nicotine may be in the blood in sufficient quantities but there was an additional amount of substance released which antagonizes the primary actions of nicotine. Such a substance may be histamine which is known to reduce coronary vascular resistance,[23] and this may serve to reduce any effect of nicotine. These possibilities can be verified by determination of nicotine in the blood. Until a sensitive method becomes available, it is important to question the exclusive use of nicotine in the understanding of the coronary effects of tobacco.
>
> The systemic absorption of substances from the lungs exposed to cigarette smoke initiated stimulation of the sympathetic nervous system with an elevation in aortic blood pressure and positive inotropic action on the heart muscle. The latter was accompanied by an elevation in coronary vascular resistance, although the perfusing blood was not exposed to cigarette smoke. Both the changes in coronary vascular resistance and myocardial contractility are indications of generalized increase of sympathetic nervous activity. If the coronary artery was not perfused, the coronary vasomotor effect would have been masked by an actual elevation in aortic pressure and the entrance of catecholamines released from the adrenal medulla so that the end result would have been an actual increase in coronary blood flow. This conforms to the general conclusion in an earlier paper[24] that the cardiac effects of tobacco arise almost entirely from the extracardiac actions of smoking instead of a direct response of the heart.

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Coronary Blood Flow in Subjects with Coronary Heart Disease

The effect of cigarette smoking on coronary blood flow was studied in patients with coronary heart disease (*79*). As was seen in normal subjects, significant increases in heart rate, arterial pressure, and cardiac output were noted. In contrast to the normal individuals studied, patients with coronary heart disease distinctly showed a much less significant compensatory increase in their coronary blood flows. These results were confirmed by a later study (*16*), using the Rubidium 84 method to estimate coronary blood flow. This study also showed that in the coronary patients studied, there was no adequate compensatory increase in coronary blood flow to meet the increased myocardial tissue demand for oxygen. Coronary blood flow apparently decreased as a result of cigarette smoking, in this particular study group of coronary patients. Although the decreases noted were not marked, they were statistically significant, and indicated that a difference existed between these coronary patients as compared to the normal subjects studied.

A difference in the coronary blood flow response to nitroglycerine has also been demonstrated in normal subjects compared to subjects with coronary heart disease. This was shown in studies using the nitrous oxide (*18*, *44*) and the Rubidium 84 (*15*) methods to measure coronary blood flow. In response to nitroglycerine the normal individuals generally increased their coronary blood flow significantly, but the coronary patients generally did not.

Animal studies have also demonstrated the decreased ability of atherosclerotic coronary arteries to increase coronary blood flow, as compared to the coronary arteries in normal animals (*94*). Dogs with experimentally produced coronary artery insufficiency also show this decreased ability (*12*). Similar differences between animals with normal coronary arteries as compared to atherosclerotic coronary arteries have been demonstrated in response to ergonovine (*80*).

The above studies indicate that the effect of nicotine upon the cardiovascular system, mediated in part by the action of released catecholamines, is generally to increase heart rate and cardiac output, and to raise systemic arterial pressure temporarily. Findings concerning the effect of nicotine on coronary blood flow are presently thought to be largely due to the indirect effects of nicotine upon the cardiovascular system. Other animal studies indicate that there may be a direct action of nicotine on the coronary vasculature to increase coronary vascular resistance, thus tending to reduce coronary blood flow. There are no human studies on the direct action of nicotine by itself on the coronary vasculature; such studies, involving the direct injection of nicotine into diseased human coronary arteries, might be dangerous. Normal individuals apparently can increase their coronary blood flows to compensate for the increased myocardial tissue oxygen demand, but apparently some patients with coronary heart disease cannot, as shown by their response to smoking.

Thus some patients with coronary heart disease may be at a particular disadvantage when smoking and under other stresses since their coronary arteries apparently cannot dilate to supply blood flow adequate to meet the increased oxygen demand associated with nicotine-induced catecholamine release. The interaction of the above effect with recent findings concerning carbon monoxide, described in the next section, may be especially important in those individuals with coronary heart disease. The present studies indicate that the effect of cigarette smoking on coronary blood flow, in the presence of preexisting coronary heart disease, may, in part, contribute to the increased incidence of acute myocardial infarctions that have been observed to be associated with cigarette smoking. No relationship between the smoking effect on coronary blood flow and the pathogenesis of coronary atherosclerosis per se is presently suggested. Additional research is needed.

(79) Regan, T. J., Frank, M. J., McGinty, J. F., Zoll, E., Hellems, H. K., Bing, R. J. Myocardial response to cigarette smoking in normal subjects and patients with coronary disease. Circulation: Journal of the American Heart Association (New York) 23(3): 367–369, March 1961.

(18) Brachfeld, N., Bozer, J., Gorlin, R. Action of nitroglycerin on coronary circulation in normal and in mild cardiac subjects. Circulation: Journal of the American Heart Association (New York) 19: 697, 1959.

(44) Gorlin, R., Brachfeld, N., MacLeod, C., Bopp, P. Action of nitroglycerin on coronary circulation in normal and in mild cardiac subjects. Circulation: Journal of the American Heart Association (New York) 19: 705, 1959.

(15) Bing, R. J., Rennish, A., Blumchen, G., Cohen, A., Gallagher, J. P., Zaleski, E. J. The determination of coronary flow equivalent with coincidence counting technic. Circulation: Journal of the American Heart Association (New York) 29:833–846, June 1964.

(94) Travell, J., Rinzler, S. H., Katz, D. Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. Annals of the New York Academy of Sciences 90: 220–231, Sept. 27, 1960.

(12) Bellet, S., West, J. W., Müller, O. F., Manzoli, U. C. Effect of nicotine on the coronary blood flow and related circulatory parameters. Correlative study in normal dogs and dogs with coronary insufficiency. Circulation Research 10(1): 27–34, January 1962.

(80) Rinzler, S. H., Travell, J., Katz, D. Detection of coronary atherosclerosis in the living animal by the ergonovine stress test. Science (Washington) 121: 900, 1955.

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Carbon Monoxide Effect

The gaseous phase of cigarette smoke contains about 4 percent carbon monoxide. This quantity can increase the levels of carboxyhemoglobin saturation of cigarette smokers from 2 percent to 10 percent (*21*). The average nonsmoker, depending on environmental exposure, usually has less than 2 percent carboxyhemoglobin saturation (*10*). Since smokers of one pack or more a day may have chronically elevated carboxyhemoglobin levels of more than 4 percent (*9*), there may be appreciable differences in the carboxyhemoglobin levels between some heavy cigarette smokers and nonsmokers.

In addition to displacing oxyhemoglobin, carbon monoxide effects a shift in the oxygen-hemoglobin dissociation curve (*2, 3, 4 5, 6*). This may result in a decreased release of oxygen at the tissue level. A series of studies (*61, 62*) has been performed on young adults to analyze the effect of cigarette smoking on carboxyhemoglobin levels, and the consequent effect on some parameters of cardiopulmonary function. An increased post exercise oxygen debt was observed after cigarette smoking as compared to controls. This, in part, may reflect not only ventilatory disturbances but also a decreased supply of oxygen in the blood due to the carbon monoxide effect, resulting in less available oxygen to meet the increased tissue demand. Similar post-exercise oxygen debts have been noted after inhalation of enough carbon monoxide to produce comparable blood levels of carboxyhemoglobin (*21*).

The consequence of the smoking/carbon monoxide effect appears to be especially important in the myocardium where relatively more oxygen is normally extracted from the coronary circulation as compared to other organ systems. (Coronary venous blood usually has an oxygen saturation of less than 25 percent, whereas blood leaving some other organs is about 75 percent saturated with oxygen (*45*).)

Dogs were exposed to carbon monoxide to elevate their carboxyhemoglobin saturation levels (*9*). In response to inhalation of carbon monoxide there was an increase in coronary blood flow but a decrease in coronary arterial-venous oxygen differences. Patients with coronary heart disease were also studied following inhalation of enough carbon monoxide to elevate their carboxyhemoglobin saturation levels to the range of 5 to 12 percent (*9*). In response to carbon monoxide there was generally an increase in the cardiac output and the coronary blood flow in most of the patients. While the systemic arterial-venous oxygen differences varied, either increasing or decreasing, the coronary arterial-venous oxygen differences decreased, indicating a decreased oxygen extraction by the myocardial tissue despite the myocardium's increased demand for oxygen. These decreases in myocardial oxygen extraction are related to increases in the carboxyhemoglobin saturation levels. It was observed that some patients evidently could compensate by increasing their coronary blood flows adequately to supply the myocardial tissue with sufficient oxygen, as indicated by a rise in myocardial oxygen uptake in these individuals. However, the other patients with coronary heart disease, evidently more severe, could not increase their coronary blood flow rate enough to compensate for the decreased oxygen carried by the blood. This latter group of patients, even though they had increased cardiac output, had less significant increases of coronary blood flow than those noted in the first group of patients. The coronary arterial-venous oxygen differences and the myocardial tissue oxygen uptakes both decreased, indicating that the myocardial tissue oxygen demand was not being met entirely.

The reduction in the amount of oxygen available to the myocardial tissue caused by the absorption of carbon monoxide from tobacco smoke may be especially critical in persons with pre-existing coronary heart disease, especially when they cannot significantly increase coronary blood flow to compensate for increased myocardial tissue oxygen demand. The carbon monoxide effect may, in part, contribute to the increased incidence of myocardial infarctions that occur in cigarette smokers. Additional research is need[illegible].

(21) Chevalier, R. B., Krumholz, R. A., Ross, J. C. Reaction of nonsmokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. Journal of the American Medical Association (Chicago) 198(10): 1061–1064, Dec. 5, 1966.

(10) Ayres, S. M., Giannelli, S., Jr., Armstrong, R. G. Carboxyhemoglobin: hemodynamic and respiratory responses to small concentrations. Science (Washington) 149: 100–101, July 9, 1965.

(9) Ayres, S. M. Personal Communication. New York, St. Vincent's Hospital and Medical Center. [Unpublished.] June 1967.

(3) Astrup, P. Den kliniske betydning af forskydninger i oksihaemoglobinets dissociations-kurve. Nordisk Medicin (Stockholm) 76: 1039–1041. 1966.

(4) Astrup, P. Variationer i oksihaemoglobinets dissociationskurve. Ugeskrift for Laeger (Kobenhavn) 128(24): 695–701, 1966.

(5) Astrup, P. Haemmet iltafgift fra blodet og udviklingen af obliterererence arteriesygdomme. Ugeskrift for Laeger (Kobenhavn) 128(24): 701–704, 1966.

(6) Astrup, P., Hellung-Larsen, P., Kjeldsen, K., Mellengaard, K. The effect of tobacco smoking on the dissociation curve of oxyhemoglobin. Investigations in patients with occlusive arterial diseases in normal subjects. Scandinavian Journal of Clinical and Laboratory Investigation (Oslo) 18(4): 450–457, 1966.

(61) Krumholz, R. A., Chevalier, R. B., Ross, J. C. Cardiopulmonary function in young smokers. A comparison of pulmonary function measurements and some cardiopulmonary responses to exercise between a group of young smokers and a comparable group of nonsmokers. Annals of Internal Medicine (Philadelphia) 60(4): 603–610, April 1964.

(62) Krumholz, R. A., Chevalier, R. B., Ross, J. C. Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence. Annals of Internal Medicine (Philadelphia) 62(2): 197–207, February 1965.

(45) Gregg, D. E., Fisher, L. C., Editors. Blood supply to the heart. *In:* Dow, P., editor. Handbook of physiology. Circulation. Sec. 2. Washington, American Physiology Society, 1963. Pp. 1563.

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Exercise and oxygen debt. It should be noted that the subjects were healthy without heart disease. The increased postexercise oxygen debt was observed in subjects using a a bicycle ergometer which increases the oxygen consumption 20 to 25 fold:

(not cited) Chevalier et al. (1963) from 300 to 5,833 cc/min

(64) Krumholz et al. (1964) from 300 to 7,900 cc/min.

Such enormous increase in oxygen consumption is not encountered in ordinary work.

This paragraph implies that since carbon monoxide inhalation increases postexercise oxygen debt and smokers also show the effect, that carbon monoxide is the cause in smokers. Reference (21) Chevalier et al. specifically stated that the pathogenesis is unknown. Their summary is as follows:

> Differences have been found in the cardiopulmonary responses to exercise between young male cigarette smokers and nonsmokers. The present study was undertaken in an attempt to determine the cause of such differences. Since smokers carry a chronically elevated carboxyhemoglobin level (>4%), carbon monoxide was inhaled by nonsmokers to raise their carboxyhemoglobin level to the range seen in a control group of smokers. This maneuver caused the development in nonsmokers of an increased oxygen debt with exercise and a reduced pulmonary diffusing capacity at rest. The changes after carbon monoxide inhalation were similar to those found when comparing smokers to nonsmokers. The pathogenesis of these changes are unknown, but support carbon monoxide as a possible etiologic factor accounting for the less efficient exercise and poorer pulmonary function performance of smokers compared to nonsmokers.

In the articles cited above, there are differences in responses to exercise of smokers and of nonsmokers inhaling carbon monoxide. The latter show slowing of the heart rate and decreased oxygen uptake during the working period; smokers show tachycardia and increased oxygen uptake.

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Studies on In Vitro *Thrombus Formation*

Recent studies have indicated that cigarette smoking may accelerate thrombus formation of human blood *in vitro*. Platelet adhesiveness, as measured by *in vitro* tests, also appears to be increased by cigarette smoking (*1, 33, 71, 87*). Other studies, comparing smokers with nonsmokers, indicate that the platelet survival time of the smokers is shortened (*73*) and the platelet turnover rate is increased (*72*). Studies of animals show there is also an increased tendency for the platelets to adhere to the vascular endothelium.

Platelet adhesiveness is reported to be increased in *in vitro* studies using the Chandler rotating loop (*32, 33, 35*); these studies generally show a consistent acceleration of the rate of thrombus formation. Other *in vitro* tests show changes in thrombus formation and some parameters of coagulation as a result of smoking (*56, 66, 87*). However, problems in experimental design and the multiplicity of tests used, measuring either the same or overlapping portions of the complicated coagulation process with varying results, cause difficulty in evaluating these results (*71*).

The mechanism of changes in characteristics of the platelets in smokers is being investigated, but there are indications that the release of catecholamines, especially epinephrine, caused by the absorption of nicotine during smoking may be intimately involved (*71, 72*). In small doses, epinephrine has been shown to promote thrombus formation and coagulation, but in large doses it inhibits these processes. Changes in the electrical charge of the platelet membrane have also been implicated in increasing platelet adhesiveness (*101*), increasing adherence to the vascular endothelium, and accelerating thrombus formation as measured by the Chandler loop method. Some of the alterations in thrombus formation may be mediated by an interaction with serum-free fatty acids and cholesterol (*70*) but current evidence suggests that inhalation of cigarette smoke acts primarily through other independent factors (*101*). Thus, cigarette smoking may cause an acceleration of the *in vitro* thrombus formation of human blood. It is reasonable to suspect that cigarette smoking, in part by affecting the thrombus-forming process in human blood, may account for some of the excess coronary heart disease deaths that occur in cigarette smokers, especially some of the deaths certified as "acute coronary thrombosis." Further research is necessary before any definite conclusion can be made.

Autopsy Studies

The two most significant pathological studies of the relationship of smoking history to atherosclerotic changes in human coronary arteries have been reported by Auerbach and Strong. Auerbach (*7*) studied 1,372 males for whom a smoking history was available and who had died of causes other than coronary heart disease. He found that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers, and that the percentage increased with amount of cigarette smoking. Both among smokers and nonsmokers the percentage of men with advanced coronary atherosclerosis also increased with age. This relationship held up even when the following were excluded: men with a history of diabetes, men who had died of any type of heart disease, and men whose hearts weighed 400 gm. or more. A matched set analysis was also carried out (reincluding some diabetics and heart disease deaths) and again the percentage of men with advanced coronary atherosclerosis was less among nonsmokers than among men who had been current cigarette smokers, and this percentage increased with the amount smoked.

Strong (*89*) in a study of coronary arteries from 645 autopsied males, 20 to 64 years of age, excluded patients with diseases he thought to be associated with smoking (emphysema, lung cancer, etc.), or with coronary heart disease (myocardial infarction, hypertension, diabetes, stroke, etc.). He found that the mean percent of coronary intimal surface occupied by raised atherosclerotic lesions was approximately twice as great in heavy smokers (25+ cigarettes/day), and about one-third greater in light smokers (less than 25/day), than in nonsmokers. Calcified lesions and mean coronary wall thickness measured radiographically were on the average highest in heavy smokers and lowest in nonsmokers. Differences among these smoking categories were generally greatest at younger ages.

These autopsy studies suggest that smoking, in addition to the acute immediate effect associated with the act of smoking, has a chronic effect leading to advanced degrees of atherogenesis. However, these findings may, in part, reflect the differences noted between smokers (*7, 89*), particularly heavy smokers, and nonsmokers in regard to greater obesity, higher dietary fat intake, and higher serum cholesterol levels. Further analyses of autopsy series are needed to determine the independent effects of cigarette smoking on atherogenesis.

(33) Glynn, M. F., Mustard, J. F., Buchanan, M. R., Murphy, E. A. Cigarette smoking and platelet aggregation. Canadian Medical Association Journal (Toronto) 96: 548-553, September 1966.

(71) Murphy, E. A., Personal communication. University of Colorado, February 1967.

(87) Sodani, B. K., Joshi, K. C. Effect of cigarette and biri smoking and tobacco chewing on blood coagulation and fibrinolytic activity. Indian Heart Journal (Calcutta) 17: 238-242, July 1965.

(73) Mustard, J. F., Murphy, E. A. Effect of smoking on blood coagulation and platelet survival in man. British Medical Journal (London) 1(5334): 846-849, Mar. 30, 1963.

(72) Murphy, E. A., Mustard, J. F. Tobacco and thrombosis. American Journal of Public Health and the Nation's Health (New York) 56(7): 1061-1073, July 1966.

(32) Engelberg, H. Cigarette smoking and the *in vitro* thrombosis of human blood. Journal of the American Medical Association (Chicago) 193: 1033-1035, Sept. 20, 1965.

(35) Engelberg, H., Futterman, M. Smoking and acceleration of the thrombotic coagulation of blood (Abstract). Circulation: Journal of the American Heart Association (New York) 33-34 (Supplement 3): 56-57, October 1966.

(34) Engelberg, H., Futterman, M. Cigarette smoking and thrombotic coagulation of human blood. Archives of Environmental Health (Chicago) 14: 266-270, February 1967.

(56) Kendal, M., Korolko, A. Tobacco smoking and blood clotting. Bulletin of Polish Medical Science and History (Chicago) 8: 145-143, October 1965.

(66) Lisiewicz, J. Badania Doswiadczalne Wplywu Palenia Papierosow Czas Krzepniecia Krwi i Osocza Uwapnionego Oraz Czas Protrombinowy i Trombinowy Osocza u Ludzi. Polski Tygodnik Lekarski (Warsaw) 18: 1471-1473, 1963.

(101) Weiss, E., Schmeltzer, H. Activity of nicotine and inactivity of lobeline and kallidin in aggregation of blood platelets. Nature (London) 207: 871-872, Aug. 21, 1965.

(70) Mutchison, I. E., Pitt, T. Effects of cigarette smoking on serum-lipid, blood-glucose, and platelet adhesiveness. Lancet (London) 2: 132-135, July 1966.

(7) Auerbach, O., Hammond, E. C., Garfinkel, L. Smoking in relation to atherosclerosis of the coronary arteries. New England Journal of Medicine (Boston) 273(15): 775-779, Oct. 7, 1965.

(89) Strong, J. P., McGill, H. C., Jr., Richards, M. L., Eggen, D. A. Relationship between cigarette smoking habits and coronary atherosclerosis in autopsied males. Circulation: Journal of the American Heart Association (New York) 33-34 (Supplement 3): 31, October 1966.

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The first group of cited references relate to the acute effects of smoking and do not compare smokers and nonsmokers. Even (72) Mustard and Murphy did not compare smokers and nonsmokers but used the same 7 subjects, all heavy smokers who refrained from smoking for at least three weeks. The interpretation of the results should consider the emotional factors involved in abstaining and resuming smoking which are known to influence platelet adhesiveness. The authors accept this possibility which they could not exclude.

Subjects.—A varied group of seven white male veterans was studied. Their ages (given in Table II) ranged between 35 and 72. Three had sustained myocardial infarctions, two cerebrovascular accidents, and one had had recurrent thrombophlebitis, but there had been no overt episodes of vascular disease in any of the patients for some months before the experiment was done. The seventh subject had chronic bronchitis and emphysema without evidence of vascular disease. All were moderately heavy smokers (at least 20 cigarettes a day), but all agreed to refrain from smoking for three weeks immediately prior to one test as well as during the 10 days during which the test was done. Although we cannot be absolutely certain that none of them lapsed occasionally, we are at least certain that their cigarette consumptions were greatly reduced.

Diet.—A diet of uniform composition and caloric content was maintained throughout. The weight of each subject was maintained constant to within 2 lb. (0.9 kg.). The diets had the following composition: fat 22% of calories, protein 15%, carbohydrate 63%. The diets contained no dairy fat or egg yolk except for 7 oz. (200 ml.) of skim milk daily; 30% of the fat was derived from vegetable sources.

Experimental Design.—This was a simple crossover design, three of the subjects selected at random being studied during the non-smoking period first and the smoking period second, and the remaining four in the reverse order. Since the same subjects were studied in the two periods no problem of comparability arises, and comparisons can be made by pairing the results.

These considerations by no means exhaust the possibilities about the means by which smoking influences platelet survival. For example, psychomotor activity is one of the factors which we have not been able to control. We have no evidence bearing on this or on what effect (if any) this may have on platelet economy.

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Smoking and Atherosclerosis. The Letter to the Editor by Burch and Rowell (Br Med J, 23 April, 1966) would be pertinent to examine, relevant to the association between atherosclerosis and smoking.

Smoking and Atherosclerosis

SIR,—You discuss in your leader (26 March, p. 755) the positive association between cigarette smoking and cardiovascular disease. We shall suggest that this is a particular example of a widespread phenomenon.

The sex- and age-distributions[1] of various categories of cardiovascular disease (International Abridged List, 1955: A85, B22, B25, B26—arteriosclerotic and degenerative heart disease—B27, B28, and B29) are all consistent with the view[1,2] that these several diseases have a disturbed-tolerance autoimmune aetiology. This interpretation is supported by the obliterative vascular changes that are observed in kidney homotransplants and which have been attributed to a host-versus-graft reaction.[3] According to the autoimmune theory the cardiovascular disease process is initiated by a small number (generally less than 10) of somatic gene mutations in lymphoid stem cells.[4-6] These spontaneous gene changes initiate the growth of one or more forbidden-clones[4,7] of cells that synthesize autoantibodies. When the target tissue lies behind a blood-tissue barrier the primary autoantibodies are necessarily humoral, and it appears[4,8] that they generally migrate on electrophoresis with the α_2-globulin serum protein fraction. When the target tissue is normally freely infiltrated by small lymphocytes these cells carrying cell-bound autoantibodies act as the primary pathogenic agents. Given this approach, disturbances in the β- and γ-globulin fractions do not represent the primary cause of spontaneous (as opposed to experimental) autoimmune disease but the body's complex response to it.[4,8]

Between the initiation of a forbidden-clone and the first manifestation of symptoms or signs a latent period inevitably intervenes. When the primary autoantibodies are cell-bound (lymphocytic), then on the average this interval, for a given environment, is about twice as long in females as in males; but when the target tissue lies behind a blood-tissue barrier the average latent period is usually of about equal duration in the two sexes.[4,5,9] From the clinical evidence we deduce[4,5,9] that the length of the latent period is determined in part by the operation of an intrinsic defence mechanism, which in the case of lymphocytic autoimmunity at least is mediated through immunoglobulins. Forbidden-clones are "foreign" and autoantigenic, and they elicit a classical immune response that restrains their proliferation. Probably all disturbed-tolerance autoimmune diseases can be precipitated and exacerbated by extrinsic factors such as certain infective agents and certain drugs.[5,8] Mental stress produces similar effects.[5,8] We have proposed that these several factors either compete for or affect the level of the defence against forbidden-clones.[5,6] Smoking probably acts in the same way. Anticenic and not-self materials entering the body have to be opsonized and phagocytized, and they therefore compete for the finite defence resources. Consequently, the efficiency of the defence against autoantigenic forbidden-clones is diminished. Autoantibodies increase in number, and the latent or chronic autoimmune condition is precipitated or exacerbated.

The idea that the intrinsic defence mechanism in autoimmunity is vulnerable to various extrinsic factors also accounts for the urban-rural differences that are found in connexion with many chronic conditions: the greater pollution of the urban atmosphere and the greater stress of urban life encourage the growth of forbidden-clones. In our view the effect of cigarette-smoking on cardiovascular disease processes is more appropriately described as exacerbating rather than causal.—We are, etc.,

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4. Burch, P. R. J., and Rowell, N. R., *Quart. Rev. Biol.*, 1965, 40, 252.
5. —— and Rowell, N. R., *Acta dermato-venereol. Stockh.*, 1965, 45, 168.
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7. —— *Brit. med. J.*, 1965, 1, 318.
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SMOKING AND CEREBROVASCULAR DISEASE

An increasing amount of evidence has accumulated in the past few years relating the development of clinical cerebrovascular disease to cigarette smoking. Most of this information has come from the prospective mortality studies.

Hammond has reported the following data from his large prospective study (47), noted in table 15.

TABLE 15.—*Cerebral vascular lesions. Age-standardized death rates, by type of smoking (lifetime history) and age at start of study*

	Age			
	45-54	55-64	65-74	75-84
	CVL death rates per 100,000 person-years			
MEN				
Never smoked regularly	28	92	349	1,358
Pipe, cigar	25	100	369	1,371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1,165
Total	35	116	391	1,272
WOMEN				
Never smoked regularly	18	57	229	1,032
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
	CVL mortality ratios			
MEN				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar	.89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	.73
Cigarette only	1.50	1.41	1.37	.86
WOMEN				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

SOURCE: E. C. Hammond (47).

Between the ages of 45 and 74 the death rates from stroke for male smokers were 37 to 50 percent higher than those for male nonsmokers of comparable age. In female smokers the death rates from stroke were 38 to 111 percent greater than those for nonsmokers. Above the age of 74 the differences between the two groups were much less.

The data in Table 16 concerning smoking and death rates from stroke are derived from the U.S. veterans study (52).

TABLE 16.—*Mortality ratios and death rates for stroke as underlying cause among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages)	1.00	1.51	1.42	1.70	1.59
Death rates:					
Age 55 to 64	59	92	112	125	130
Age 65 to 74	280	323	312	382	502

SOURCE: U.S. veterans study (52).

When stroke was certified as the principal cause of death, the death rates for smokers were higher than for nonsmokers; however, no pronounced increase was noted in the mortality ratios as the degree of smoking increased. The death rates from stroke for all ages was 59 percent higher in heavy smokers (40 or more cigarettes) than in nonsmokers.

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TABLE 17.—*Mortality ratios and death rates for stroke as the underlying or contributory diagnosis among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages)	1.00	1.45	1.45	1.75	1.83
Death rates:					
Age 55 to 64	101	152	174	195	2 6
Age 65 to 74	424	514	520	616	724

Source: U.S. veterans study (55).

Stroke, listed as either the underlying or contributory cause of death on the death certificate, was also associated with progressively increasing mortality ratios and death rates as the extent of smoking increased. Heavy smokers here had an 83 percent greater mortality from stroke than nonsmokers.

Mortality data by underlying cause of death may often be misleading, particularly when stroke is concerned. Many stroke patients have concomitant coronary heart disease, or may develop pneumonia and other complications that may hasten death. The death certificate may carry stroke as the underlying cause or as the contributory cause of death, depending upon the interpretation of the physician at the time. The important addition of these data is that smoking is associated with a higher mortality from stroke, whether the stroke is recorded as either the underlying cause or as the contributory cause of death.

These two studies indicate that smoking may be associated with a higher mortality from stroke in the relatively younger age groups (under age 74). More than one-half the strokes that occur each year are in the group above age 75 and in this group there is no evidence relating smoking to cerebrovascular disease.

Another large study has been conducted analyzing the mortality of 50,000 former students who entered Harvard University or the University of Pennsylvania during the years 1916–50 (*74, 75, 76*). From this population 171 deaths from cerebrovascular accidents have been identified. A review of the medical records from their college years has been carried out, and selected factors were correlated with the later occurrence of stroke. Seven precursive "risk factors" present at the time of college attendance have been defined: Cigarette smoking, high blood pressure, excess body weight, short stature, a history of early parental death, a history of nonparticipation in college sports, and a history of "heart consciousness" (also shown to be correlated with coronary heart disease). Cigarette smoking and a history of early parental death were more strongly correlated with thrombotic stroke than with hemorrhagic stroke. Students who smoked more than 10 cigarettes daily were at twice the risk of having a fatal stroke than were those who smoked less or not at all.

In 1965 the Framingham study (*54*) reported that while an excess development of thrombotic brain infarction appeared to be associated with cigarette smoking, statistically significant differences could not be demonstrated with the small number of cases available at that time. More recent data from Framingham indicates that cigarette smoking increases the risk of stroke in males. The relatively small number of women smokers had too few strokes for adequate analysis.

The new epidemiological evidence, then, indicates that cigarette smoking may be more closely associated with cerebrovascular disease in the population between the ages of 45 and 74 years than was previously indicated. If cerebrovascular thrombosis (thrombotic brain infarction) accounts for this association, it is possible that some of the considerations of how cigarette smoking may produce coronary thrombosis also apply to the pathogenesis of cerebrovascular disease. Further research is essential to understand the relationships that exist between cigarette smoking and cerebrovascular disease.

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PAFFENBARGER, R. S., JR., WING, A. L. Characteristics in youth predisposing to fatal stroke in later years. Lancet (London) 1: 753-754, Apr. 8, 1967.

(54) KANNEL, W. B., DAWBER, T. R., COHEN, M. E., MCNAMARA, P. M. Vascular disease of the brain—epidemiologic aspects: The Framingham study. American Journal of Public Health and the Nation's Health (New York) 55(9): 1355–1366, September 1965.

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Additional information on mortality data concerning aortic aneurysm has been provided by the U.S. veterans study (*52*) and the Hammond (*47*) studies, as noted in tables 18 and 19, respectively.

TABLE 18.—*Mortality ratios and age-standardized death rates for aortic aneurysm in U.S. veterans, current smokers of cigarettes only*

	Number of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio	1.00	2.12	5.53	5.95	7.28
DEATH RATES					
Age:					
55 to 64	6	13	27	43	44
65 to 74	25	57	123	157	221

Source: U.S. veterans study (*52*).

TABLE 19.—*Mortality ratios and age-standardized death rates for aortic aneurysm*

	Age 45-64 years		Age 65-79 years	
	Females	Males	Females	Males
Mortality ratio	3.89	2.62	3.33	4.92
Death rates	[1] 4(*1*)	18(*7*)	43(*15*)	118(*24*)

[1] Numbers in parentheses indicate death rates of those who never smoked regularly.

Source: Hammond, E. C. (*47*).

It is apparent that there is a close association between cigarette smoking and death caused by aortic aneurysms.

Thus, the additional evidence confirms the previously observed association between cigarette smoking and death due to nonsyphilitic aortic aneurysm.

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The Health Consequences of SMOKING

1968 SUPPLEMENT TO THE
1967 Public Health Service Review

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

CHAPTER 1

Smoking and Cardiovascular Diseases

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INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 Report. Brief mention of the conclusions of the 1964 Report and the highlights of the 1967 Report is made to facilitate an understanding of the significance of the most recent information. The current research findings should be considered in the perspective of the research evidence previously presented in the 1964 (*148*) and 1967 (*146*) Reports.

Conclusions of the 1964 Report (*148*)

Male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance.

Highlights of the 1967 Report (*146*)

1. Additional evidence not only confirms the fact that cigarette smokers have increased death rates from coronary heart disease, but also suggests how these deaths may be caused by cigarette smoking. There is an increasing convergence of many types of evidence concerning cigarette smoking and coronary heart disease which strongly suggests that cigarette smoking can cause death from coronary heart disease.
2. Cigarette smoking males have a higher coronary heart disease death rate than nonsmoking males. This death rate may, on the average, be 70 percent greater, and in some, even 200 percent greater or more in the presence of other known "risk factors" for coronary heart disease. Female cigarette smokers also have a higher coronary heart disease death rate than do nonsmoking females, although not as high as that for males. In general, the death rates from this disease increase with amount smoked. Cessation* of cigarette smoking is followed by a reduction in the risk of dying from coronary heart disease when compared with the risk incurred by those who continue to smoke.
3. A greater frequency of advanced coronary arteriosclerosis is noted in male cigarette smokers, especially in those who smoke heavily.
4. Additional evidence strengthens the association between cigarette smoking and cerebrovascular disease, and suggests that some of the pathogenetic considerations pertinent to coronary heart disease may also apply to cerebrovascular disease.

*Those who have stopped smoking cigarettes have a lower risk of dying from coronary heart disease than those who continue to smoke.

SMOKING AND CORONARY HEART DISEASE

Coronary Heart Disease Mortality

As in the past two decades, coronary heart disease in the United States continues as the leading cause of death, being responsible in 1967 for 567,710 deaths or 31.0 percent of the total of 1,833,900 deaths.

Since age specific data are not yet available for 1967, table 1 shows the number of deaths due to coronary heart disease and the death rates per 100,000 persons by age for 1966.

Table 1.—*Coronary heart disease deaths and death rates per 100,000 population, by age: United States, 1966*

[Disease category 420 in the ICD Manual, 1955]

Age	Number of deaths	Death rates
Total	573,191	292.7
Under 25 years	250	0.3
25–34 years	1,469	6.6
35–44 years	12,522	52.0
45–54 years	45,997	206.3
55–64 years	99,647	577.3
65–74 years	162,555	1,405.2
75–84 years	171,737	2,979.5
85 and over	78,854	7,015.5
Not stated	160	(X)

X—Not applicable.

Source: Monthly Vital Statistics, National Center for Health Statistics (147).

These data illustrate the dramatic increase in death rates as age advances, with the increase being particularly marked after age 15. The death rates for coronary heart disease for men and women continue to show a conspicuous difference. In 1966 it was 361.6 for males and 226.5 for females per 100,000 population.

(148) U.S. Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service, Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(146) U.S. Public Health Service. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication No. 1696, 1967. 227 pp.

(147) U.S. Public Health Service. National Center for Health Statistics. Monthly Vital Statistic Report. Final Mortality Statistics 16(2) (Supplement): 1–12, March 12, 1968.

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While several studies of various aspects of the association between coronary heart disease mortality and cigarette smoking have been reported during the past year, the most significant studies of this association are contained in the 1967 report.

The several new studies of various aspects of the association between coronary heart disease mortality and cigarette smoking follow.

Friedman (*46*) reported a strong positive correlation between per capita cigarette sales and coronary heart disease death rates by states. The correlation is 0.76 when data only from those states with relatively accurate information of cigarette consumption are analyzed. Related factors such as urbanization or softness of the local water supply do not explain this degree of association.

Other studies deal with the excess deaths associated with smoking. Strobel, et al. (*149*) reported that among 3,479 Swiss physicians, over 50 percent of the excess deaths occurring over a 9-year period among smokers was due to coronary heart disease.

In contrast to the study above and data from the United States in which approximately one-half of the excess deaths associated with smoking are attributed to cardiovascular causes (*143*), preliminary data from Hirayama (*65*) show that the excess deaths in Japan associated with smoking were primarily explained by cancer of various sites. Only 12 percent of the excess deaths were associated with cardiovascular causes. This prospective study of 265,118 adults over the age of 40 encompassed a followup period of 15 months. Additional follow-up by Hirayama should yield useful data with respect to smoking and excess mortality from cardiovascular diseases in this Japanese population group, particularly with regard to the younger adults in the study.

Hyams, et al. (*67*), on the other hand, speculate that the apparent increase in the occurrence of coronary heart disease among Japanese males, especially under the age of fifty, may be due to a trend toward Westernization in both diet and smoking habits among younger Japanese men.

Hammond (*54*), in his prospective study of over 1 million men and women, showed a positive relationship between the duration of the smoking habit and coronary heart disease mortality. In the Framingham Heart Study (*71*), no association was found between the duration of the smoking habit and the incidence of mortality from heart attacks among men who were "heavy smokers" (more than one package of cigarettes per day).

These discrepancies between the relationship of smoking to the incidence of total coronary heart disease and mortality from acute coronary heart disease may be accounted for, in part, by the differences in population groups studied and by the possibility that duration of smoking may have a greater association with the fatal forms of coronary heart disease.

Kannel, et al. (*70*), in more recent data from the Framingham study, indicate that the fatal and more severe forms of coronary disease are more strongly associated with cigarette smoking that the less severe forms (figure 1).

(46) Friedman, G. D. Cigarette smoking and geographic variation in coronary heart disease mortality in the United States. Journal of Chronic Diseases 20: 769-779. 1967.

(149) Strobel, M., Gsell, O. Mortalität in Beziehung zum Tabakrauchen: 9 Jahre Beobachtungen bei Ärzten in der Schweiz. Helvetica Medica Acta 32(6): 547-593. December 1965.

(65) Hirayama, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center Research Institute, September 1967. 14 pp.

(67) Hyams, L., Segi, M., Archer, M. Myocardial infarction in the Japanese. A retrospective study. American Journal of Cardiology 20(4): 548-554. October 1967.

(54) Hammond, E. C. Smoking in relation to the death rates of 1 million men and women. In: Haenszel, W., editor. Epidemiological Approaches to the Study of Cancer and Other Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 127-204.

(71) Kannel, W. B., Dawber, T. R., McNamara, P. M. Detection of the coronary-prone adult: The Framingham Study. Journal of the Iowa Medical Society 56(1): 26-34, January 1966.

(70) Kannel, W. B., Castelli, W. P., McNamara, P. M. The coronary profile: 12-year follow-up in the Framingham study. Journal of Occupational Medicine 9(12): 611-619. December 1967.

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Coronary Heart Disease Morbidity *

Much of the morbidity data reported during this past year resulted from retrospective studies of patients or cross-sectional studies (*106, 107, 127, 131, 151*). In these studies the findings revealed that there

* Also may include mortality data in this presentation.

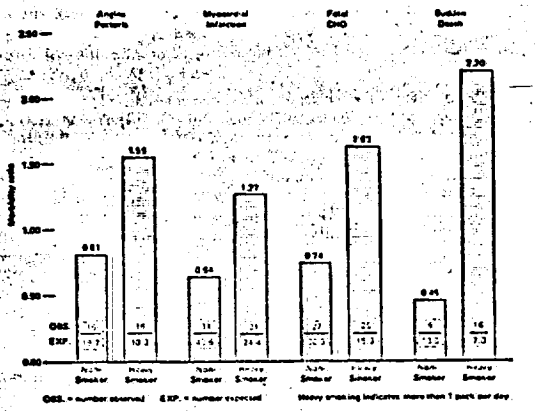

FIGURE 1—Morbidity ratios for specified manifestations of coronary heart disease, among men aged 50–59 years at entry into Framingham Heart Study, classified by smoking habit: 12 years' experience.

SOURCE: Kannel, et al. (70).

were relatively more smokers among the groups with coronary heart disease, than among the comparison, or control groups.

In a retrospective study of myocardial infarction patients in Japan, Hyams, et al. (67) reported similar findings, particularly among the men under age 50. Differences measured by an exposure index combining intensity and duration of smoking showed the same trend, though the data were not statistically significant.

Dorken (*30, 31*) reported on two retrospective studies in Hamburg, Germany: one, a study of female patients; the other, a study of male patients. He concluded that there is a strong association between smoking and myocardial infarction in both males and females under the age of 45.

In Dublin, Mulcahy, et al. (*106, 108, 109*) studied groups of male and female coronary heart disease patients under age 60. He found that a much greater portion of the patients, in comparison with a sample of the general population, smoked cigarettes. Also, the intensity (amount multiplied by duration) of smoking was as much as 2½ times greater among the male patients and 3 times greater among the female coronary heart disease patients as contrasted with the males and females in the general population.

In a study of 675 aviators, smoking histories taken in 1963 did not show a positive association in the prevalence of coronary heart disease with either amount, duration, or intensity of smoking. These findings are based on 38 cases (5.7 percent) of coronary heart disease of all forms among a very select population and are therefore subject to large sampling variations (*96*). Moreover, since smokers may have an excessive mortality during an acute myocardial infarction, as mentioned before, prevalence rates are not as good a measure of the association between smoking and coronary heart disease as are incidence rates.

Epstein (*39*), although finding no prevalence differences between smokers and nonsmokers in his Tecumseh Study, found an increased incidence in cigarette smokers of both fatal and nonfatal coronary heart disease.

In a short prospective study of 11,000 Norwegian men (12,000 with smoking histories), Natvig (*113*) did find an increased risk of incidence of first myocardial infarction or angina pectoris among those men 50–59 years of age who smoked.

Since the 1967 Report, the continuing prospective epidemiologic studies leave somewhat clarified the differential relationship between smoking and each of the manifestation categories of coronary heart disease: angina, nonfatal myocardial infarction, fatal myocardial infarction and sudden death.

(106) MULCAHY, R., HICKEY, N. J. Cigarette smoking habits of patients with coronary heart disease. British Heart Journal 29: 404–408, 1966.

(107) MULCAHY, R., HICKEY, N. J. The role of cigarette smoking in the causation of atherosclerosis. Geriatrics 22(2): 165–174, February 1967.

(127) ROTH, O., ERNST, A., WOLFF, G. D. Long range observations in fifty thirty young patients with myocardial infarction. American Journal of Cardiology 19(3): 331–338, March 1967.

(131) SILVERS, M. I. Myocardial infarction among southwestern Americans: Indians. Annals of Internal Medicine 67(4): 806–807, October 1967.

(151) VELLIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen Infarktpatienten und Kontrollpersonen in der Ostschweiz. Schweizerische Medizinische Wochenschrift 96(23): 748–758, June 11, 1966.

(30) DÖRKEN, H. Die Rauchgewohnheiten bei Jüngeren Frauen mit Herzinfarkt. Münchener Medizinische Wochenschrift 109(41): 2129–2134, January 1967.

(31) DÖRKEN, H. Die Rauchgewohnheiten bei Jüngeren Herzinfarkt-Patienten. Münchener Medizinische Wochenschrift 109(4): 187–192, January 27, 1967.

(108) MULCAHY, R., HICKEY, N. J., MAHER, B. J. The aetiology of coronary heart disease in women. Journal of the Irish Medical Association 60 (335): 23–29, January 1967.

(109) MULCAHY, R., HICKEY, N. J., MAHER, B. J. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. Circulation 36(4): 577–586, April 1967.

(96) LANE, N. E., ORLEBAR, A. The thousand aviator study: Smoking history correlates of selected physiological, biochemical, and anthropometric measures. U.S. Naval Aerospace Medical Institute, NAMI-951. Under the Joint sponsorship of the U.S. Public Health Service, and the National Aeronautics and Space Administration, NASA Order R-136, April 27, 1966. 12 pp.

(39) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine 60(1): 4–8, January 1967.

(113) NATVIG, H. Effekten av umettede fettsyrer på hyppigheten av hjerteinfarkt M.fl. Resultatet av befolkningsgenes "oljeforsøk." Tidsskrift for den Norske Laegeforening 87(11): 1033–1041, June 1967.

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Data from the Framingham Heart Study (*69*) revealed that "heavy" cigarette smoking, more than 20 cigarettes per day, is positively associated with uncomplicated angina in males but not in females (figure 2).

Similar findings were reported by Weinblatt (*155*) in a study of male subjects in the Health Insurance Plan with the associations more pronounced among those men who smoked two or more packages of cigarettes per day. As can be seen, in table 2, the arithmetic differences in rates between smokers and nonsmokers are greater for myocardial infarction than for angina; however, the risk ratios are similar.

In a retrospective study, Heyden-Stucki et al. (*61*) found no association of smoking with angina or other chest complaints.

The inconsistencies in data on the association between smoking and the development of angina may be due in part to differences in methods used to diagnose and classify angina and to record smoking habits in these epidemiologic studies. Further standardization in this area may help to determine more accurately the relationship of smoking to angina.

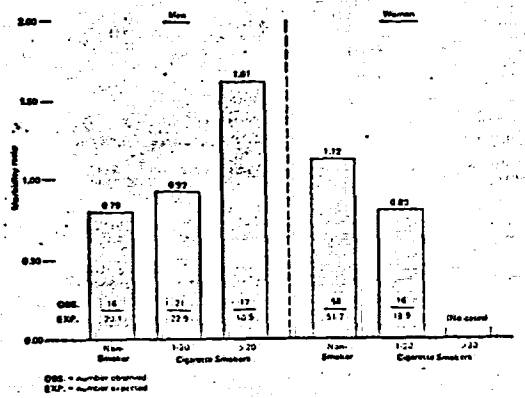

FIGURE 2—Angina pectoris morbidity ratios among persons aged 30–59 years at entry into Framingham Heart Study, classified by sex and number of cigarettes smoked: 12 years' experience.

SOURCE: Kannel, et al. (*69*).

TABLE 2.—*Age-adjusted incidence rates per 1,000 males aged 35–64, and morbidity ratios, for specified manifestations of coronary heart disease, by smoking category: Health Insurance Plan Study*

[5 year observation data]

Smoking category	Myocardial infarction		Angina	
	Incidence rate	Morbidity ratio	Incidence rate	Morbidity ratio
Current nonsmokers	3.27	1.0	1.37	1.0
Current cigarette smokers	7.01	2.1	2.62	1.9
Less than 2 packs	5.05	1.5	2.03	1.5
2 or more packs	20.80	6.4	6.64	4.8

SOURCE: Weinblatt, E. (*155*).

In the Western Collaborative Study, Rosenman et al. reported higher rates of silent myocardial infarctions in younger men, and higher rates of recurrent myocardial infarctions at all ages among those who smoked more than 25 cigarettes per day (*123, 124*).

Friedemann, et al. (*44*) reported reinfarctions occurred more frequently among smokers than nonsmokers.

Dorken (*29*) found in a series of 550 men of all ages, in Hamburg, who survived at least 5 and up to 6 years after their first myocardial infarction, that 172 (52 percent) had stopped smoking completely after the first infarction. In contrast, of 85 subjects who had died from a second myocardial infarction or sudden coronary death after leaving the hospital, only 25 (29.2 percent) had given up smoking completely ($P<0.001$).

(69) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis: The Framingham Study. In: Wynder, E. L., Hoffmann, D., editors. Toward A Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(155) WEINBLATT, E. Personal communication. April 1968.

(61) HEYDEN-STUCKY, S. SCHIELA-REICH, S. Cardiologische Risikofaktoren bei Schweizer Mannern. Schweizerische Medizinische Wochenschrift 97 (1): 20–25, January 7, 1967.

(123) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Clinically unrecognized myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 776–782, June 1967.

(124) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Recurring and fatal myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 771–775, June 1967.

(44) FRIEDEMANN, M., STEIN, H., EMMRICH, J., REINERT, H. Der Herzinfarkt in Atiologischer und Katamnestischer Sicht. Deutsches Archiv fur Klinische Medizin 214: 264–286, 1963.

(29) DORKEN, H. The etiology of myocardial infarction—with special reference to cigarette smoking among young coronary patients and those with second heart attacks. In: Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

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Relationships of Cigarette Smoking to Other Risk Factors

The ongoing prospective and other epidemiologic studies have yielded findings which permit analysis of the interrelationships among cigarette smoking and other factors considered to increase the risk of coronary heart disease.

Age

Generally, the findings show that the incidence rate of coronary heart disease increases with age, both among smokers and nonsmokers. The morbidity ratio of coronary heart disease in smokers versus nonsmokers decreases with age though the absolute number of excess deaths among smokers increases with age.

High Blood Pressure

Recent reports on the relationship between smoking and blood pressure appear to support the findings in the 1967 report:

> Although the inhalation of cigarette smoke is frequently accompanied by acute transient elevations in blood pressure, habitual smokers tend to have lower blood pressures than do nonsmokers. But, given the presence of high blood pressure in an individual, smoking acts as an additional risk factor for the development of coronary heart disease.

Heyden-Stucki et al. (*61*) report that among 500 workers in Switzerland, smokers, particularly heavy smokers, have lower blood pressure as a group than do nonsmokers. Smokers also were found to have normal or subnormal weights in contrast to nonsmokers who had a greater mean weight; thus, confounding the relationship between smoking and blood pressure level. Tibblin (*144*) in a cohort study of Scandinavian men born in 1913, found a lower mean blood pressure among smokers than among nonsmokers. As the population was classified according to levels of blood pressure, a step-wise decrease in the prevalence of smoking was noted as the level of blood pressure increased. A similar trend for both systolic and diastolic pressures was also reported by Clark, et al. (*23*) as shown in table 3.

Table 3.—*Mean age and mean systolic and diastolic blood pressure, by smoking category: Los Angeles Heart Study, 1963*

Current cigarette smoking status			Blood pressure (mm. of Hg.)	
	Number of subjects	Years of age	Systolic	Diastolic
Smokers	407	54	133.6	82.5
Nonsmokers	725	57	137.0	83.9

Source: Clark, V. A. (*23*).

In the study of 675 aviators (*96*) smoking intensity, although not found to be associated significantly with systolic or diastolic blood pressures, was positively associated with pulse pressure. Reid, et al. (*122*) in a comparative study of workers in Great Britain and the United States noted lower diastolic blood pressures among smokers than among nonsmokers in both groups; adjustment for weight variations reduced this difference appreciably.

Mulcahy (*107*), in a retrospective study of 100 women coronary heart disease patients under 60 years of age, reported that 50 to 60 percent had diastolic hypertension (>90 mm Hg.). Hypertension and cigarette smoking, together or separately, were present in over 80 percent of these patients.

In the major prospective studies, when both smoking and hypertension were present, an interactive increase in the risk of developing coronary heart disease was noted. When to these two risk factors elevated cholesterol levels were added, the risk of developing coronary heart disease was further increased (figures 3 and 4).

(144) Tibblin, G. High blood pressure in men aged 50—A population study of men born in 1913. Acta Medica Scandinavica (Supplementum 470): 1–81, 1967.

(23) Clark, V. A., Chapman, J. M., Coulson, A. H. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. Journal of Chronic Diseases 20: 571–581, 1967.

(122) Reid, D. D., Holland, W. W., Rose, G. A. An Anglo-American cardiovascular comparison. Lancet 4(7531): 1375–1378, December 30, 1967.

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Hypertension and Smoking. The article by (107) Mulcahy does not contain any information on hypertension. There are 77 women reported to have coronary heart disease and their smoking habits were matched with statistics of the general female population. The relevant paragraph and Table are as follows:

Table 2 illustrates the smoking experience of the 77 female patients with classical CHD under 60 years who were seen by us. The numbers are small and further study is clearly needed, but already we can identify a significant deficiency of nonsmokers and ex-smokers among our female patients compared

Table 2 Ratio of smokers to nonsmokers in 77 female patients under 60 years with CHD compared to estimated ratio in general female population for age group 35 to 59 in 1961

Category	Present enquiry		Female population* (age group 35-59)	
	No. of patients	%	No. of subjects	%
Smokers	49	64	261	45.6
Ex-smokers	1	1	52	9.1
Nonsmokers	27	35	259	45.3
Total	77	100	572	100

Significant at the 1% level

*Source: "Statistics of Smoking in the Irish Republic," Research Services, Limited, Dublin, 1962

to the general female population. Also, our 77 patients are on average more than 2½ times heavier smokers than the general Irish female population of the same age group.

Our finding of a significant association between cigarette smoking and CHD in women confirms the findings of M. F. Oliver of Edinburgh[4] who noted an excess of smokers and a deficiency of nonsmokers and ex-smokers among 50 women less than 45 years of age with cardiac infarction. He found little or no connection between cigarette smoking and angina pectoris among young women. Our 23 females with angina pectoris had a lighter smoking experience than the 54 with cardiac infarction or acute coronary insufficiency, but nevertheless they had a heavier experience than the general population.

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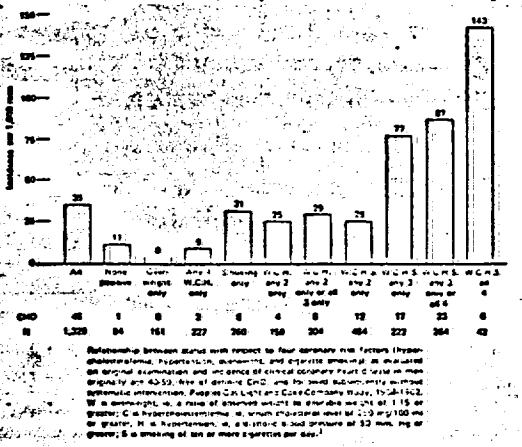
Source: https://www.industrydocuments.ucsf.edu/docs/jslk0000

Certain of the retrospective and cross-sectional studies (*62, 151*) have, in general, demonstrated higher cholesterol levels in smokers than in nonsmokers. Pincherle, et al. (*119*) and Lane, et al. (*96*) report similar findings. A study by Heyden-Stucki (*61*) of 500 Swiss workers found a similar trend but the differences between smokers and nonsmokers with respect to cholesterol levels and other lipids were not statistically significant.

A recent report (*36*) describes some of the variability of interrelationships among smoking, blood pressure and cholesterol levels in different population groups throughout the world. It concludes that though nonsmokers tend to be heavier and have higher blood pressure levels than cigarette smokers, heavy smokers tend to be in the top



Relationship between status with respect to four coronary risk factors (hypercholesterolemia, hypertension, overweight, and cigarette smoking) as evaluated on original examination and incidence of clinical coronary heart disease in men originally age 40-59, free of definite CHD, and followed subsequently without systematic intervention. Peoples Gas Light and Coke Company Study, 1958-1962. W is overweight, i.e., a ratio of observed weight to desirable weight of 1.15 or greater; C is hypercholesterolemia, i.e., serum cholesterol level of 250 mg/100 ml or greater; H is hypertension, i.e., a diastolic blood pressure of 90 mm. Hg or greater; S is smoking of ten or more cigarettes per day.[1]

FIGURE 3—Incidence of coronary heart disease among men aged 40–59 years at entry into Peoples Gas Light and Coke Company Study, classified as to presence of specified risk factors: 1958–1962.

SOURCE: Stamler, et al. (*138*).

deciles for blood pressure and relative weight. Cholesterol-smoking relationships described in these studies do not show a consistent pattern.

In a controlled dietary intervention study of postinfarction patients Leren (*97*) found that smoking habits did not influence the serum cholesterol level or the coronary heart disease relapse rate in the control group. Among the study group of dieters there was a suggestion, although not statistically significant at the 0.05 level, that smokers had a higher coronary heart disease relapse rate than nonsmokers.

(*62*) HEYDEN-STUCKY, S. Epidemiologie des Herzinfarktes 1965. Schweizerische Medizinische Wochenschrift 95(45): 1535–1540, November 6, 1965.

(*119*) PINCHERLE, G., WRIGHT, H. B. Screening in the early diagnosis and prevention of cardiovascular disease. Journal of the College of General Practitioners 13: 280–289, 1967.

(*36*) Epidemiological studies related to coronary heart disease: Characteristics of men aged 40–59 in seven countries. F. Smoking habits. Acta Medica Scandinavica (Supplement 460): 304–315, 1967.

(*138*) STAMLER, J., BERKSON, D. M., LEVINSON, M., LINDBERG, H. A., MOJONNIER, L., MILLER, W. A., HALL, Y., ANDELMAN, S. L. Coronary artery disease. Status of preventive efforts. Archives of Environmental Health 13(3): 322–335, September 1966.

(*97*) LEREN, P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. Acta Medica Scandinavica (Supplement 466): 1–92, 1966.

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Physical Inactivity

The independent and combined effects of cigarette smoking and physical activity, as described in the 1967 report, continue to be demonstrated as more data are accumulated. The apparent protective effect of physical activity appears to be more pronounced with regard to myocardial infarction than angina [table 4, *(155)*]. Differences in methods of assessment of history of physical activity in case versus

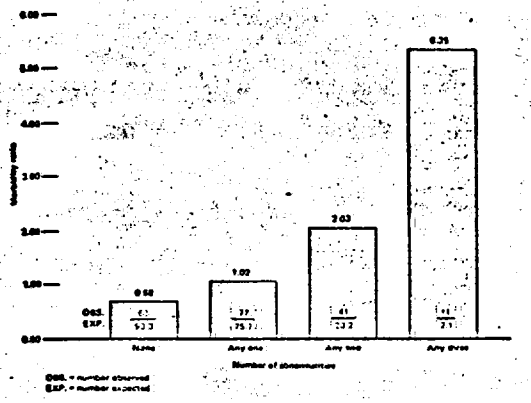

FIGURE 4—Myocardial infarction morbidity ratios among men aged 30–59 years at entry into Framingham Heart Study, classified according to presence of selected risk factors: 12 years experience (Risk factors are: cholesterol level over 250 mg/100 ml., systolic blood pressure over 160 mm. Hg., smoking over 1 pack of cigarettes per day).

SOURCE: Kannel, et al. *(70)*.

control groups may account for some differences in the incidence rates noted.

Blackburn, et al. *(10)* found no relationship of smoking to the prevalence of postexercise ECG changes in a study of 10,200 men age 40 to 59 years. However, there were only 510 (5.1 percent) subjects with a "positive" ECG response.

Sociological, Psychological and Personality Variables

Two studies *(35, 64)* demonstrated an inverse relationship between the frequency of coronary heart disease and the educational level of the subjects. In the Bell Telephone System *(64)*, those men without a college education had higher coronary heart disease rates than those with a college education. Also, those not attending college tended to smoke more.

In a study of factors related to coronary heart disease among Cleveland attorneys *(35)*, the quality of the law schools attended by the sub-

TABLE 4.—*Annual age-adjusted incidence rates of specified manifestations of coronary heart disease per 1,000 males aged 35–64 and corresponding morbidity ratios, by smoking habits and physical activity class: Health Insurance Plan Study*

[8 year observation data]

Smoking status and physical activity class	Myocardial infarction		Angina	
	Incidence rate	Morbidity ratio	Incidence rate	Morbidity ratio
All current nonsmokers	3.27	1.0	1.37	1.0
Not cigarette smokers:				
Least active	6.33	1.9	2.14	1.6
Intermediate	3.07	0.9	1.67	1.2
Most active	3.01	0.9	1.32	1.0
All current cigarette smokers:				
Least active	10.59	3.3	2.31	1.7
Intermediate	5.50	1.8	2.93	2.1
Most active	5.77	1.8	2.74	2.0
Less than 2 packs:				
Least active	7.61	2.3	2.05	1.5
Intermediate	4.71	1.4	2.37	1.7
Most active	3.85	1.2	1.93	1.4
2 or more packs:				
Least active	39.09	12.0	4.97	3.6
Intermediate	11.27	3.5	5.09	3.7
Most active	24.09	7.4	12.29	8.9

(10) BLACKBURN, H., KEYS, A., KARVONEN, M., VAN BUCHEM, F. S. P., TAYLOR, H. L. Relation of "positive" postexercise electrocardiographic responses to other characteristics of risk. Circulation 36(4) (Supplement II): 70. October 1967.

(35) FRIEDMAN, E. H., HELLERSTEIN, H. K. Occupational stress, law school hierarchy, and coronary artery disease in Cleveland attorneys. Psychosomatic Medicine 29(1): 72–86, January–February 1967.

64. HINKLE, L. E., JR., WHITNEY, L. H., LEHMAN, E. W., DUNN, J., BENJAMIN, B., KING, R., PLAKUN, A., FLEHINGER, B. Personal Communication, 1968.

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Postexercise ECG Changes. The observations of (10) Blackburn et al. are very important because they relate to the incidence of myocardial ischemia in 10, 260 men. That 519 subjects had positive ECG response should not deter from the significance of the investigation. The reference is actually an abstract which is not normally cited as a primary source of information. Hower the 1968 document is full of abstracts and personal communications.

Relation of "Positive" Postexercise Electrocardiographic Responses to Other Characteristics of Risk

Henry Blackburn, Ancel Keys, Minneapolis, Minnesota, Martti Karvonen, Helsinki, Finland, F. S. P. Van Buchem, Haarlem, The Netherlands, and Henry L. Taylor, Minneapolis, Minnesota. Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minnesota

The electrocardiographic response to exercise has become a powerful tool for identifying greatly increased risk of acute coronary episodes in otherwise "healthy" individuals. It is now necessary to establish how much it really adds to information over and above already known factors of risk. This was first examined by a study of the interrelations of a "positive" exercise ECG response with other measurable physical characteristics and habits. It is best studied in natural populations which contain realistic proportions of "positive" and "negative" responders and broad ranges of characteristics. Here the frequency of 519 "positive" responses among 10,260 men aged 40 to 59 years was plotted according to increasing obesity, blood pressure, and serum cholesterol, and activity and smoking habits.

The test was a standard three-minute, constant-rate step, and criteria for "positive" tests were rigidly defined. The most important association was a linear relationship between frequency of "positive" ECG responses and level of systolic blood pressure ($P < 0.0001$ between lowest and highest pressure classes). No relation of exercise response to fatness was found through the bulk of the distribution, but among the upper 20% of men ranked by skinfold thickness the rate of "positive" responses was significantly greater ($P < 0.001$ between lowest and highest obesity classes). There was a decreasing rate of "positives" with increasing physical activity class and no relationship to serum cholesterol or smoking habit. Evaluation of the prognostic power of the exercise ECG requires, at the least, consideration of age, sex, blood pressure, and obesity.

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ject were ranked independently by a law school professor. Lawyers attending schools in the "highest law school quality group" had lower rates of coronary heart disease than those attending schools in the "lower law school quality group." Also, those in the latter group had started smoking at an earlier age. Since additional differences were noted for other risk factors, smoking alone may not be responsible for the total differences in these rates. In both studies, it was hypothesized that with respect to susceptibility to development of coronary heart disease, behavior patterns and attitudes established prior to professional training and prior to stresses resulting from job mobility and job tension, were more significant than the later stresses which resulted from their present jobs.

Recent data from the Western Collaborative Group Study (*125*) appear to show that among men 39–49 years of age, cigarette smoking was associated with several coronary heart disease risk factors (table 5). Though these findings may be statistically significant, the differences between smokers and nonsmokers were small.

TABLE 5.—*Age-adjusted means for selected coronary heart disease risk factors and personal characteristics, by smoking category: Western Collaborative Group Study, males 39–49 years of age*

[8½ years average observation data]

Variable	Smoking category		Percent difference
	Never smoked	Smoked 25 cigarettes or more per day	
Serum cholesterol	217.2	231.8	+6.7
Beta/alpha ratio	1.9	2.1	+10.5
Lipalbumin	21.1	19.4	−8.1
Systolic blood pressure	126.3	129.9	+2.9
Diastolic blood pressure	82.0	81.3	−0.9
Ponderal index	12.6	12.7	+0.8
Physical activity on job	1.95	1.95	0
Amount of exercise	2.18	2.05	−6.0
Income	2.75	2.75	0

Source: Rosenman, R. H. (125).

TABLE 6.—*Percent distribution by behavior type of smokers and nonsmokers: Western Collaborative Group Study, males 39–49 years of age*

[8½ years average observation data]

Behavior type	Total	Smoking category					
		Never smoked	Former smokers	Current 1–24 cigarettes per day	1–15 cigarettes per day	16–25 cigarettes per day	26 cigarettes or more per day
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Type A	47.5	41.3	45.0	48.3	44.8	48.9	56.7
Type B	52.5	58.7	55.0	51.7	55.2	51.1	43.3

Test of difference of distributions: $X^2 = 26.70$; df = 3; $p = .001$.

Source: Rosenman, R. H. (125).

Behavioral pattern type A is characterized by an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency as contrasted to type B. There was a difference in the distribution of personality types A and B among smokers and nonsmokers (table 6).

The foregoing data refer to concurrent observations gathered in 1960–1961 on 3,182 men who were then free of manifestations of coronary heart disease. A follow-up of this population during the next 4½ years disclosed that cigarette smokers experienced substantially higher rates of coronary heart disease than those who had never smoked. This finding is based on data for men 39–49 years of age, which have been adjusted for the confounding influences of related risk factors, such as age, cholesterol, etc. (table 7).

(125) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., ZYZANSKI, S. J. Personal Communication, 1968.

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TABLE 7.—*Incidence of new coronary heart disease by smoking category: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Smoking category	Number of men	Rate per 10,000 population	
		Adjusted for concomitant variables	Not adjusted
Never smoked	340	38	29
Former cigarette smokers	241	67	92
Pipe and cigar only	406	27	16
1–15 cigarettes	212	51	52
16–25 cigarettes	436	89	92
26 cigarettes and over	425	93	104

SOURCE: Rosenman, R. H. (115).

The coronary heart disease rate for those men smoking 26 or more cigarettes a day is seen to be about three times greater than for those who never smoked. The rate for former smokers is still rather high, even after adjustment for concomitant variables. The largest impact of the adjustment procedure is noted among this group, and suggests that those who quit may have done so because they were already a relatively high-risk group for reasons other than smoking. The relatively low rate among men smoking only pipes and cigars is noted in this as in other prospective studies.

The nature of the association of smoking and coronary heart disease incidence among type A and type B personality groups is not easy to characterize or interpret. Among the type A group, the pipe and cigar smokers and the light cigarette smokers had the lowest rates of incidence of new coronary heart disease, while the highest rates were found among those smoking 26 or more cigarettes a day. For the type B group, the lowest rates occurred among those who had never smoked, and the highest among the light cigarette smokers. The age-adjusted rates of new incidence of coronary heart disease per 10,000 men 39–49 years of age are shown in table 8.

Additional data to permit concomitant analysis of these variables and those in table 7 are needed.

TABLE 8.—*Incidence of new coronary heart disease by smoking category and behavior type: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Smoking category	Rate per 10,000 population	
	Behavior type A	Behavior type B
Total	91	33
Never smoked	53	13
Former smokers	107	36
Pipe and cigars only	18	36
Cigarettes:		
1–15	18	60
16–25	135	33
26 and over	149	51

SOURCE: Rosenman, R. H. (115).

Lane, et al. (96) found significant relationships of smoking intensity and duration with personality factors—impulsiveness, emotional instability and belligerence scales.

Thomas (142) after reviewing various studies of psychological variables related to coronary heart disease, concludes that smoking may have different effects on different personality types and at different anxiety levels.

Multiple Risk Factors

The acceptance of a multiple factor causation hypothesis for coronary heart disease emphasizes the need for more sophisticated statistical analyses of appropriate data. Our understanding of the relative importance of various risk factors from the limited number of such special analyses has not been altered significantly from that obtained by more conventional statistical analyses (38).

Clarification of the apparent independence of several of the major risk factors has resulted.

Truett, et al. (145) emphasize that the major risk factors are noted to have a different order of importance by age and sex. Cigarette smoking is particularly important among younger males as noted in table 9.

(142) THOMAS, C. B. On cigarette smoking, coronary heart disease, and the genetic hypothesis. Johns Hopkins Medical Journal 122(2): 69–76, February 1968.

(38) EPSTEIN, F. H. Predicting coronary heart disease. Journal of the American Medical Association 201(11): 795–849, September 11, 1967.

(145) TRUETT, J., CORNFIELD, J., KANNEL, W. A multivariate analysis of the risk of coronary heart disease in Framingham. Journal of Chronic Diseases 20: 511–524, 1967.

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Review of Psychological and Personality Variables. The sentence describing the (143) Thomas article does not do justice to her excellent discussion. The article is reproduced in its entirety because it discusses another way of interpreting association between cigarette smoking and coronary heart disease.

ON CIGARETTE SMOKING, CORONARY HEART DISEASE, AND THE GENETIC HYPOTHESIS[1]

CAROLINE BEDELL THOMAS

Department of Medicine, The Johns Hopkins University School of Medicine

Received for publication September 14, 1967

What is the basis for the association between cigarette smoking and coronary heart disease? Although coronary disease is the most frequent cause of death in the United States today, and the majority of men smoke cigarettes, the answer to this question is still obscure. In 1956, Doll and Hill reported a significant statistical relationship between cigarette smoking and death from coronary disease which has been confirmed by other prospective studies (1–8). The difference between smokers and nonsmokers in respect to coronary disease mortality is relatively small, however, compared to the ten- to twentyfold differences often noted in respect to deaths from lung cancer in the prospective studies reviewed by the Advisory Committee to the Surgeon General of the Public Health Service (9, page 161, Table 5). In contrast, the median mortality ratio for coronary disease was 1.7 (range 1.5 to 2.0) for seven prospective studies of smokers and nonsmokers (9, page 323).

Many people have concluded that a causal relationship between cigarette smoking and coronary disease has, therefore, been established, but some have pointed out that such an association could be equally well explained on the grounds that 1) smokers are constitutionally different from nonsmokers, so that smoking cigarettes gives them more of a physiological or psychological boost and 2) cigarette smokers are more often the precoronary type of individual than nonsmokers. There have been scattered pieces of evidence that this may, indeed, be the case (10–16). At the time of the Surgeon General's report, these were sufficient to warrant the statement that "male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance." (9, page 327).

In examining the evidence that the statistical association between cigarette smoking and coronary heart disease may not be a simple cause-and-effect relationship, two facets of the genetic hypothesis,

1) that cigarette smokers are constitutionally different from nonsmokers, and
2) that individuals with a high risk of developing coronary heart disease are constitutionally different from those with a low risk,

can profitably be considered together. Although the implications are basically genetic, the term "constitutional" is used here rather than "genetic" because most measurements of adult men, whether physical or psychological, represent the phenotype, or manifest characteristics of the individual resulting from the interaction of his genotype, or genetic make-up, and the environment. The degree to which the environment interacts with the genetic component varies greatly according to the trait under consideration and the particular external circumstances. Certain traits, such as the blood groups, are not known to be modifiable by natural means. Others, such as stature, are modified only under

[1] This work was supported by Research Grant HE-01891, National Institutes of Health.

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such adverse conditions as severe undernutrition, while the proportionate roles played by genetics and environment in such characteristics as body weight, arterial blood pressure, total serum cholesterol level and personality structure are still being vigorously debated (17–29). While the genetic hypothesis does not necessarily contradict the various environmental hypotheses, it does limit them and diminish their importance by asserting that not all individuals are equally susceptible to adverse environmental influences.

Reports of actual genetic studies in this area are limited in number. Differences have been found in the distributions of such genetic markers as the blood groups and the ability to taste phenylthiourea (P.T.C.) in populations of smokers and nonsmokers; these findings are in harmony with the genetic hypothesis (12, 15). Twin studies carried out abroad point in the same direction. Monozygotic twins showed a higher degree of concordance than dizygotic twins in regard to smoking habits (30). In monozygotic twins with discordant smoking habits, coronary disease was not more frequent among the smokers than among the nonsmokers (31, 32). The numbers involved in these comparisons were too small, however, for definitive statistical evaluation.

Somatic variables reported to show statistically significant smoker-nonsmoker differences range from a series of anthropometric measurements to resting heart rate and blood pressure (13, 14, 16). The mean differences in all of these comparisons have been small, however, and at times have varied in direction from study to study, as in the case of weight (14, 16). Moreover, the small circulatory differences observed could well be the *result* of the smoking habit rather than a true constitutional difference.

Perhaps the most thought-provoking smoker-nonsmoker differences lie in the psychological area. There is a considerable body of evidence to show that the personality of smokers differs from that of nonsmokers in important ways (33–38). In the words of Eysenck, 1) "smokers tend to be more emotional, more neurotic, more given to anxieties, more tense, more likely to suffer from the so-called psychosomatic symptoms" than nonsmokers, and 2) "smokers tend to be more extroverted, nonsmokers more introverted.—Extroverted people tend to be sociable, to like parties, to value good food, drink and the good things of life generally—to take risks more readily, to act without regard to consequences, and to find it difficult to stick to the same task day after day" (39). Schubert has emphasized the point that the smoker seeks physiological, social and psychological arousal (40). His findings among college students, based on the Minnesota Multiphasic Personality Inventory, revealed that, compared with nonsmokers, smokers more frequently describe themselves as 1) being bored and seeking thrills, 2) behaving in a socially unacceptable fashion, and 3) having masculine traits. Smokers also scored higher on an impulsivity scale.

Work from our own laboratory indicates that psychological smoker-nonsmoker differences are of considerable importance. As part of a long-term prospective study of the precursors of hypertension and coronary disease, discriminant function analysis was used to test the hypothesis that cigarette smokers are different from nonsmokers in a number of psychobiological ways (41). The overall differentiation between nonsmokers and two groups of cigarette smokers in a population of male medical students was found to be highly significant.

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Cigarette smokers had substantially greater *anxiety* scores[2] than nonsmokers; *heart rate* and *anxiety* showed the greatest discriminatory powers among the seven variables used. *Cholesterol* and *pulse pressure* contributed to the differentiation to a lesser degree, with *anger* close behind. These findings, taken with those of others cited above, suggest that outstanding characteristics differentiating cigarette smokers from nonsmokers reside in the realm of personality.

It was, therefore, intriguing to find that *anxiety* was the most important variable in a similar discriminatory analysis based on parental history of coronary heart disease (43). Virtually the same population and variables were used; in particular, the measure of *anxiety* employed in the two analyses was identical. Again, the overall differentiation was highly significant. On the average, the group with *fathers* affected by coronary heart disease reported a *higher* anxiety level than did the group with both parents unaffected, whereas the group whose *mothers* had coronary heart disease had *lower* anxiety scores than the group with two unaffected parents. *Depression* was significantly less evident in both positive-parent groups. Although they aided in the discrimination, *anger, diastolic pressure, height* and *cholesterol level* made much smaller contributions.

From these two discriminatory analyses, several striking points emerge:

1. the same psychological characteristic, *anxiety,* was an important single variable in differentiating cigarette smokers from nonsmokers and in distinguishing subjects with a positive parental history of coronary disease from subjects without such a history,
2. the two criterion groups of smokers, which were selected on a quantitative basis in respect to number of cigarettes smoked a day, did *not* have significantly different characteristics from each other, and
3. the two groups with a positive parental history of coronary disease fell on opposite sides of the negative parental coronary disease group in respect to their mean anxiety scores.

Since a rather simply-derived anxiety scale proved to be a highly significant variable in both the smoker-nonsmoker differentiation and the discrimination between groups with and without parental coronary disease, the interesting possibility is raised that the link between cigarette smoking and coronary heart disease has to do with *anxiety* under stress. Does other research about the coronary personality tend to support this hypothesis?

More than twenty years ago, Dunbar described the personality profile of patients with coronary occlusion as one of compulsive striving, with an urge to get to the top through hard work, self-discipline and mastery of others (44). Her sub-

[2]Anxiety scores were based on the answers given by 1085 medical students to a questionnaire specially devised for the Study of the Precursors of Hypertension and Coronary Disease (41, 42). The questionnaire consists of a list of 25 habits of nervous tension (HNT); the subject was asked to check all the reactions or types of behavior characteristic of him when under stress. Patterns of response to stress were determined by means of a phi correlation matrix; scales were derived from the HNT items showing the highest degrees of association with each other. The reactions comprising the anxiety scale consist of *anxious feelings, general tension, difficulty sleeping, loss of appetite, tremulousness* and *urge to confide*, all of which showed significant positive correlations, and *urge to eat*, which was negatively correlated (41, p. 180). The anxiety scale scores, therefore, ranged from +6 to −1.

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jects were hospitalized patients under the age of 55. She came to her conclusions through psychiatric interviews supplemented by the Rorschach Test.

Since that time, there has been little agreement in regard to a psychodynamic personality pattern associated with coronary disease (15). There are some indications, however, that there may be *two* major coronary personality patterns which are diametrically opposed to each other. Bahnson and Wardwell, using home interviews plus self-administered check lists, studied 32 white men aged 35–64, who had survived their first attacks of myocardial infarction, and compared them with a control group (16). They found some differences between the coronary patients and the control group in respect to their feelings and attitudes toward their parents. The coronary group, however, resolved itself into two discrete subgroups which were almost the opposite of each other: the self-oriented, regressive type corresponding to the mother-oriented coronary patient ($N = 19$) and the socio-centric and controlled type corresponding to the father-oriented patient ($N = 13$).

The mother-oriented group showed the following characteristics:

1. they identified with their mothers in terms of her personal manners and intimate behavior identification
2. they were among the younger coronary patients
3. they were passive, stating that they frequently day-dreamed or "sat and did nothing", often lacking interest in and commitment to work
4. they showed dependency by tending to turn to others for help when in trouble
5. they were not compulsive and showed little concern over "face"
6. they had strong succorant needs
7. they had low ego strength and self-acceptance
8. they were unstable in that they often felt mixed-up, tense and worried
9. they showed a trend toward anxiety and depression
10. they frequently made use of regressive defenses
11. they showed insufficient control of aggression.

The father-oriented patients, on the other hand, showed the following characteristics:

1. they identified with their fathers through somatic and social image identification
2. they were among the older coronary patients
3. they were active and self-reliant
4. they showed strong compensatory socio-centric needs for achievement
5. they had considerable self-control and ego strength, with high self-acceptance and self-esteem
6. they clung to social norms
7. they had concern over "face"
8. they resorted frequently to the use of compulsive and repressive defenses in order to perform as solid citizens in spite of an unsatisfactory underlying self-image
9. their social commitment represented a flight from themselves.

Both the mother-oriented and the father-oriented coronary patients were considered by the authors to have failed in establishing their own identities in a satisfactory manner.

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In 1964, Ostfeld and his co-workers reported a four-year follow-up of a prospective epidemiological study of coronary heart disease in which the Minnesota Multiphasic Personality Inventory and the 16 Personality Factor Questionnaire were used to obtain measures of personality in men 40–55 years of age at the start (47). They found personality differences between the 48 men who, since being registered in the study, had developed symptoms of angina pectoris and the 37 men who had had myocardial infarctions. (They did not give the mean ages of their groups). On the average, the 1771 men who had remained free of clinical coronary disease showed personality profiles which lay *between* the angina pectoris group and the myocardial infarction group. Their findings indicated that the men in the angina group complained significantly more about somatic symptoms of all sorts and worried significantly more about the state of their health, even in the absence of objective findings, than the men in the infarct group. The angina group also reported greater lability in cardiovascular functioning and greater emotional lability and suggestibility. When the non-coronary group was compared with the total coronary group, no significant differences were found in their MMPI scores, but the 16 PF indicated that the coronary group were more independent in their social relationships, more suspicious of the motives of other people, and had greater feelings of inner tension.

A prospective study of coronary heart disease was initiated in 1960 by the Western Collaborative Group (8). Friedman and Rosenman, the leaders, had previously described an oral psychological questionnaire by which the specific behavior pattern of a subject could be classified as Type A or Type B. They considered that Type A was the coronary behavior pattern. It is characterized by excessive drive, aggressiveness, ambition, competitiveness and a sense of time urgency. They described Type B, on the other hand, as the relative absence of these characteristics. Answers to this questionnaire were part of the comprehensive data collected at intake on over 3,000 subjects. After two years, 54 of 1,584 Type A men and 16 of 1,593 Type B men had developed coronary heart disease, more than a threefold difference. After four and a half years, there is still a predominance of the Type A behavior pattern among the subjects who developed coronary disease, but the difference is less striking (48). It should be noted that a substantial number of Type B men *did* develop coronary disease; again the evidence suggests that at least two precoronary personality types are involved.

That there are at least two major types of coronary disease has been suggested by clinical studies, also. In two groups of men dying from coronary heart disease, for example, those diagnosed as having coronary disease at their last periodic health examination were compared with those whose heart disease was undetected at that time (49). The latter group was younger, and contained nearly twice as many heavy cigarette smokers and nearly twice as many men with hypercholesteremia as did the group with diagnosed heart disease. The facts that 1) both hypercholesteremia and heavy cigarette smoking have been more closely associated with death from coronary disease at younger than at older ages (cf. Table 20, p. 1105, ref. 6, 8, 49); 2) the anxiety-linked "coronary personality" was more often found in younger coronary patients by Bahnson and Wardwell, and 3) the preponderance of new coronary events in Type A subjects was greatest in

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Rosenman and Friedman's youngest age group, all tend to support Oliver's statement, "Indeed, there may be at least two major types of coronary disease—one associated with an active metabolic disorder and another associated with advancing age" (50).

Much remains to be done before the psychological factors underlying either the smoking habit or the coronary diathesis are fully understood, but it looks more and more as if the *kind of person* one is has to be taken into account. Whereas a decade ago, Hammond said, "there is as much reason to suppose that cigarette smoking causes nervous tension as to believe that nervous tension causes cigarette smoking," it now seems possible that both statements are true, but for different types of men, so that one uses smoking as an energizer, the other as a tranquillizer (51). Our own findings and those of others point to the existence of distinctive personality traits in cigarette smokers, on the one hand, and in precoronary individuals and coronary patients on the other. Inasmuch as a specific pattern of *anxiety* under stress was significantly related both to cigarette smoking and to parental coronary disease, *anxiety* appears to be one kind of common denominator (41, 43). In three studies, anxiety has been described as characterizing one of *two* groups of coronary patients or precoronary individuals—the *mother-oriented group* of Bahnson and Wardwell (46), the *angina group* of Ostfeld et al (47) and the *Type A behavior* pattern of Friedman and Rosenman (8). The familial occurrence of coronary heart disease has been documented, and points toward the involvement of genetic factors (52, 53). It seems likely that smoking habit patterns, too, are, to some extent, expressions of inborn differences. Intensive investigation of the sources and kinds of anxiety, and how destructive forms of anxiety can be identified and relieved may be the next important step in the prevention of coronary heart disease.

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Genetic and Constitutional Studies

Baer (*5*) found that heavy smokers among college males were taller than light smokers and nonsmokers. Lane, et al. (*56*) also found significant associations between body size measurements, including ponderal index (though not with height or weight individually), and amount of smoking in the study of over 675 aviators.

TABLE 9.—*Linear discriminant function coefficients (in standard units) for various risk factors in coronary heart disease, by sex and age: 12 Year Framingham Study*

Risk factors	Men				Women		
	Combined ages	30-39 years	40-49 years	50-62 years	Combined ages	30-49 years	50-62 years
Age	0.5931	0.2394	0.3331	0.2370	0.6259	0.7323	0.2600
Cholesterol	0.4444	0.9613	0.3207	0.3790	0.2841	0.7322	0.1207
Systolic blood pressure	0.3334	0.3427	0.1669	0.3509	0.5556	0.1947	0.4776
Relative weight	0.1890	0.1911	0.3619	0.1046	0.0975	0.0751	0.1481
Hemoglobin	−0.1050	0.0313	−0.0134	−0.2206	0.0392	−0.0301	0.0734
Cigarettes smoked	0.4192	0.6823	0.5084	0.3004	0.0625	−0.0731	0.1262
ECG abnormality	0.2626	0.2653	0.2556	0.2197	0.2015	0.2231	0.2526

SOURCE: TRUSSEL, *J.* (*128*)

Cederlof (*18*) has emphasized the value of studies of twins for investigating aspects of coronary heart disease and presents certain suggested modifications in methodology. The 1967 Report (*146*) discussed the studies by Cederlof on Swedish twin pairs (*19, 20*). His data on American twin pairs was recently presented and showed results similar to those of the Swedish twins (*18*).

The problems with interpretation of these studies are several. The small numbers of cases and the combining of data for both sexes in various subcategories make rates and ratios subject to significant chance variations. In addition, use of a questionnaire for angina, with only modest levels of reliability and validity requires a larger study population before definitive conclusions can be made. The lack of information on the distribution of risk factors other than smoking in subsamples of discordant twin pairs and the total group of twin pairs makes the comparison of ratios for prevalence of symptoms difficult to evaluate. The inclusion in the "smoking" group of those who had stopped smoking up to 3 years previous to the study, would also tend to diminish the differences between smokers and nonsmokers. Definitions of discordant smoking habits must conform to those differences identified as significant in the large-scale population studies.

The fact that discordance for smoking does occur among monozygotic twins certainly indicates that the smoking habit cannot be determined by genetic factors alone. Twin studies with further sophistication of design, larger number of cases, better definitions of disease, and more significant identification of discordant exposures have the potential of contributing substantially to our understanding of the interactive factors in coronary heart disease.

In an article reviewing some of the epidemiological evidence in the 3½ years subsequent to the 1964 report, Seltzer (*129*) concluded that there was no substantial evidence to indicate a further association of cigarette smoking with coronary heart disease beyond that stated in the 1964 report.

Seltzer alluded to what he called "inconsistencies" in the recent literature relating to duration, amount, age, inhalation and mode of tobacco smoking with coronary heart disease.

The addition of many more person years of experience, from the new and continuing studies, provides data since the 1964 Report that can be analyzed age-specifically. When this is done most of these "inconsistencies" disappear.

Seltzer's conclusion is contrary to that of most epidemiologists who are familiar with the current research. Furthermore, he has not considered the important relevance of the experimental, pathological, and clinical data that have been reported since 1964 concerning cigarette smoking and cardiovascular diseases.

(*5*) BAER, D. J. Height, weight, and ponderal index of college male smokers and nonsmokers. Journal of Psychology 64: 101-105, September 1966.

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(*129*) SELTZER, C. C. An evaluation of the effect of smoking on coronary heart disease. I. Epidemiological evidence. Journal of the American Medical Association 203(3): 193-200, January 15, 1968.

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Seltzer's criticisms. The questions raised by (129) Seltzer have not been adequately answered by the 1968 document. The article is reproduced in its complete form.

An Evaluation of the Effect of Smoking on Coronary Heart Disease

I. Epidemiological Evidence

Carl C. Seltzer, PhD

In January 1964, the Surgeon General's Advisory Committee on Smoking and Health[1] in considering the available information on smoking and coronary heart disease (CHD) (International Statistical Classification [ISC] 420) reported that "male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has casual significance."

Three points should be noted. First, the committee left no doubt that there was a consistent statistically significant association among cigarette smokers of increased mortality and morbidity from CHD in men, particularly during middle life. Seven large completed or current prospective studies of smoking and death rate gave a CHD median mortality ratio (current cigarette smokers to nonsmokers) of 1.7, with no significant excess deaths among cigar and pipe smokers. Second, the committee recognized that certain factors other than smoking were known or thought to predispose to the condition or to be also associated with an increased incidence. Included among these were age, sex, morphological constitution, heredity, occupations involving responsibility and stress, low levels of physical activity, diets high in saturated fats, high blood pressure, high serum cholesterol levels, and excessive obesity. Third, the point was made that if it could be shown that cigarette smokers and nonsmokers had significant constitutional differences apart from any differences that might be caused by smoking itself, then the possibility would exist that some predisposition of smokers to the disease might also be of constitutional origin and not caused by smoking. After reviewing some of this evidence, the committee concluded, "In spite of some bits of suggestive evidence the existence of basic constitutional differences between smokers and nonsmokers is not presently established."

The Surgeon General, Luther Terry, MD, on Jan 29, 1964, speaking of CHD stated, ". . . the committee was unable to reach a firm conclusion as to the role smoking plays in causing or precipitating a death from this disease. We need to find out for sure whether smoking is a factor in this disease or whether it should be exonerated . . . we have no real clues as to what it is in tobacco that influences coronary artery disease, if indeed it does."[2]

Since publication of the Surgeon General's Report on Smoking and Health in early 1964, there have appeared many statements with regard to the

See also pages 139 and 201.

relationship of cigarette smoking and CHD which go far beyond the limited conclusions of the Surgeon General's Advisory Committee and the then Surgeon General. Some of these statements come from US Public Health officials, from responsible persons in medicine and science, and from numerous medical societies throughout the country, as well as many other sources. For example, in 1965 it was stated, "Ultimate elimination of cigarette smoking . . . would mean the saving of some 250,000 Americans from premature deaths caused by or associated with cigarette smoking . . . half of these premature deaths associated with cigarette smoking are due to cardiovascular diseases, particularly

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coronary artery disease. . . ."[1][2][3] In 1965, it was affirmed that ". . . the association [American Heart Association] believes that there is a total of approximately 250,000 excess premature deaths associated with cigarette smoking each year in the United States, and that of those, about 125,000 are associated with cardiovascular disease, principally coronary heart disease. . . . We have excellent evidence that heavy cigarette smoking, a pack or more a day, particularly accelerates atherosclerosis, and accentuates its effects, makes it worse. This accounts for the increased premature deaths that are associated with cigarette smoking so far as coronary artery disease is concerned."[4][5][6] In 1966 it was said, "In view of the mountain of evidence now available this is no longer a 'controversial' matter. The massive evidence indicating that cigarette smoking is a major coronary risk factor in middle-aged Americans and British men have been reviewed in many places . . ."[7] Again in 1966, it was declared ". . . unforgiveable for us to write off the 48 million adults in the United States who are now cigarette smokers. After all, these are the people in whom the extra hundreds of thousands of premature deaths will be occurring each year for the next 20 or 30 years; these are the people who suffer from . . . . the 300,000 extra coronaries . . ."[8]

From the statements, ". . . it is not clear that the association has causal significance" and ". . . the committee was unable to reach a firm conclusion as to the role smoking plays in causing or precipitating death from this disease . . ." of the Surgeon General and his Advisory Committee on Smoking and Health in January 1964, we have since been presented with "131,000 excess deaths," "125,000 excess premature deaths," "300,000 extra coronaries" each year that are "caused by" or "associated with cigarette smoking."

Attention should be focused on the phrases "caused by" and "associated with cigarette smoking." These phrases clearly imply that the consequences of smoking cigarettes is a variable amount of excess premature CHD deaths. But no such implication can be drawn from the conclusion of the Surgeon General's committee of 1964. The latter reported a higher death rate from CHD *among male cigarette smokers* than among nonsmokers. If one were to transcribe this statement in terms of "excess deaths," then it could be stated that there was an excess of CHD deaths *among cigarette smokers* than among nonsmokers. To shift from excess deaths *among* cigarette smokers to excess deaths *associated with cigarette smoking* is to attribute *causality* to cigarette smoking, an attribution which the advisory committee was unable to reach.

We have no reason for assuming that what we are dealing with here is a matter of semantics. Rather, the more likely event is that these statements causally linking mortality from CHD among cigarette smokers must represent conclusions reached by some from new evidence available since the issuance of the advisory committee report in 1964. It becomes important, then, to inquire into the nature of this new evidence. At the same time, it is necessary to inquire into the availability of additional new evidence bearing upon the question of genetic and constitutional factors between smokers and nonsmokers, particularly insofar as they are related to the etiology of coronary heart disease.

Some readers may object to the use of the phrase "caused by," since the words "cause and effect" are extremely difficult to define clearly. In using these words, we are following the practice of the Surgeon General's 1964 report, which attempted to explain (pp 20-21) the meaning which that committee attached to the term causality. In stating "cigarette smoking is causally related to lung cancer in men," the Surgeon General's committee implied that cigarette smoking increases the probability that lung cancer will develop in a man. With regard to cardiovascular disease, the committee stated, "it is not clear that the association has causal significance," implying that the evidence available to them was insufficient to judge whether cigarette smoking is an effective agent in increasing the probability of death from cardiovascular disease or not.

Purpose of the Report

The purpose of this report, then, is to review the more important publications dealing with smoking and CHD which have appeared subsequent to the Surgeon General's Report on Smoking and Health in 1964, to answer the following question:

What is the nature of the additional evidence on smoking and CHD which has resulted in the magnification and extension of the claims of the effects of cigarette smoking on mortality and morbidity from CHD?

This particular communication (part 1) will consider the epidemiological evidence only and is limited to data on men. Subsequent reports covering experimental and clinical data, and constitutional and genetic evidence are planned.

This analysis of the epidemiological evidence was submitted for publication almost simultaneously with the appearance of *The Health Consequences of Smoking*, a Public Health Service review published in late 1967.[9] Accordingly, this is an independent analysis and does not contain references to or comparisons with the 1967 report.

The Material

In the 3½ years since publication of the Surgeon General's report of 1964, a certain amount of epidemiological research has been completed or continued in this country or abroad. For the purpose of this report, consideration has been given to the more pertinent studies as follows: Doll and Hill study of British doctors,[10] the combined Albany and Framingham study,[11] Dorn's US veterans study,[12] Hammond's prospective study,[13] the Canadian veterans study,[14] the Evans County, Georgia study,[15] the Tecumseh, Michigan prospective

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study,[11] Reid and co-workers' migrant study,[12] the health insurance plan (HIP) studies,[13,14] and the national health survey.[15]

These investigations are not always comparable, since their study designs lead to incidence rates of disease manifestations in some and to prevalence rates of disease or illness disability in others. Incidence rates of mortality or morbidity derived from longitudinal prospective or retrospective studies may be quite a different matter than prevalence rates of disease, illness, or disability derived from cross-sectional studies of whatever nature. These distinctions are important and must be kept in mind in assessing the respective findings in these studies, especially in connection with mortality ratios computed from different base lines. The first four studies listed above are prospective studies of mortality or morbidity with attendant death rates or incidence rates of disease manifestations in large populations, and hence have certain elements of comparability. On the other hand, for example, the national health survey is a prevalence study and does not identify the rate at which various types of morbidity develop in differential groups in the population but simply reports the recent existence of illness or disability, or both. As such, its findings under certain conditions may be spurious and at best are supportive in nature when they identify relationships previously established in incidence studies.

(It is to be noted, however, that "surprisingly good agreement" between prevalence and incidence results was found by the Framingham heart study with respect to relative risks for CHD.)[16]

While all of these investigations deserve detailed individual analyses of their findings, the limitations of space do not permit such elaboration. Many important discrepancies or inconsistencies (as well as consistencies) in various aspects of these studies are overlooked when the results of the studies are characterized solely by their main conclusions. A topical analysis of important aspects of the studies affords a productive approach to an understanding of the relative consistency of the results of the investigations.

Epidemiological Data Published Since Surgeon General's Report of 1964

The more important new evidence relative to mortality and morbidity from CHD is summarized according to the following subject categories: (1) overall mortality and morbidity in smokers and nonsmokers, (2) morbidity from angina pectoris, (3) mode of tobacco smoking, (4) age of smokers, (5) amount of cigarette smoking, (6) duration of cigarette smoking, (7) inhalation, and (8) disease rates in ex-smokers in relation to the duration of the cessation of smoking.

Overall Mortality and Morbidity in Smokers and Nonsmokers.—The Surgeon General's 1964 report concluded that male cigarette smokers have a higher death rate from CHD than men who did not smoke. All the new evidence gives the same results, a *confirmation* of the earlier findings. This is not surprising, since the conclusions of the 1964 report were based on "seven large completed or current prospective smoking and death rate studies." Additional new prospective studies or the extension of observations on previously reported current studies on the same or similar populations would not be expected to give different results. Similarly, all the new evidence on morbidity, with the exception of the Tecumseh study of Epstein et al,[15] confirms the existence of higher CHD prevalence rates among smokers than among nonsmokers. It is not clear why the Tecumseh study CHD prevalence rates are higher in nonsmokers than in smokers at every age level up to 70 years.

The new evidence does not change the basic nature of the association of higher CHD death rates in cigarette smokers. It simply confirms the previous evidence. The new data, either through longer observation periods of follow-up of ongoing studies or through additional studies of large populations, in the main merely serve to provide an opportunity for a more precise look at various interrelationships. Furthermore, there has been no change in the intensity of the association, such as would be suggested if the new data showed consistently higher average CHD death rates for smokers compared to nonsmokers than did the older data. But this has not been the case. The Surgeon General's 1964 report indicated a median mortality ratio of 1.7 among persons currently smoking cigarettes. It is seldom noted, however, that the Doll and Hill study of British doctors' (one of the key mortality studies) showed a 33% greater mortality rate for cigarette smokers from "CHD without hypertension" than nonsmokers, a figure far below that of most other prospective studies. But in the main, the average value of the mortality ratio in the new studies is approximately that found in the older evidence.

Angina Pectoris.—The Surgeon General's 1964 report makes brief mention of the fact that "angina pectoris . . . is less closely associated with cigarette smoking than is myocardial infarction." Available new mortality data support the conclusion that cigarette smokers have higher death rates associated with myocardial infarction than nonsmokers. But the new data appear to be ambivalent with respect to angina pectoris.

The combined Albany and Framingham study[16] clearly shows no significant increase in incidence of angina among cigarette smokers compared with nonsmokers. It was even found that the morbidity ratio (Framingham series) for those who smoked 20 or more cigarettes per day (78) was below that of the non-cigarette smokers (86). The conclusion arrived at was that "The risk of angina pectoris as the sole or initial manifestation of CHD appears to be unrelated to the tobacco habit." On the other hand, both the HIP[13] and Reid and co-workers' migrant[12] studies gave opposite results. The HIP

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study (based on incidence) reported a statistically significant association between cigarette smoking and angina pectoris among men. The authors of this study, however, caution that, "variations in methodology and diagnostic criteria may explain this departure from other studies' observation of no difference in risk for angina among cigarette smokers and nonsmokers." The migrant study, based on prevalence of angina-like symptoms, is in agreement with the results of the HIP study. It is quite probable that Epstein et al's Tecumseh study[13] also provides evidence of an absence of association between smoking and angina pectoris, since their data showed a slightly lower prevalence of CHD (angina pectoris or electrocardiographic signs of myocardial disease) in smokers.

It should be pointed out, in further reference to angina pectoris, that Cederlof et al,[14] in a study of morbidity among monozygotic twins from Sweden, found a similar frequency of angina pectoris among smokers and nonsmokers, a finding in general agreement with the data of the combined Albany and Framingham study.

Uncomplicated angina pectoris comprises about 20% of all manifestations of CHD in men; elimination of such cases would mean elimination of a significant segment of CHD cases from consideration of being related to the tobacco habit.

Mode of Tobacco Smoking.—The Surgeon General's 1964 report pointed out that ". . . the association of coronary disease with the use of tobacco in other forms [apart from cigarettes] has not been striking." All the new evidence with regard to pipe and cigar smokers showed little or no increase in their death rates from CHD over that of nonsmokers. In the case of the Doll and Hill study of British doctors,[4] pipe or cigar smokers gave a lower death rate than the group of nonsmokers. In the Dorn study of US veterans,[11] the mortality ratios of persons who smoked cigars or a pipe were virtually the same as that of nonsmokers. The Hammond study of American men[15] showed pipe smokers on the whole had lower CHD death rates than nonsmokers, while the cigar smokers tended to have slightly higher rates than the nonsmokers.

Overall, it may be said that the new evidence appears to establish a lack of association of excess deaths due to coronary heart disease among pipe or cigar smokers, a less qualified finding than given in the 1964 report. CHD disability, on the other hand, may show slightly higher frequency in pipe or cigar smokers than nonsmokers.

The fact that there appears to be no evidence for excess CHD death risk among pipe or cigar smokers is a matter of considerable importance. This result from epidemiological surveys is a disquieting finding to those engaged in the study of the effects of tobacco smoking on health. For the most part, the problem has been simply ignored, perhaps in the hope that somehow or other it would just disappear by itself. But the discordance of an excess mortality due to CHD in cigarette smokers but not in cigar or pipe smokers cannot be summarily swept under the rug.

Nicotine in the tobacco smoke is regarded by many as the agent responsible for the effects on coronary heart disease. However, this discordance in disease effects is inexplicable in terms of amount of nicotine and other constituents of tobacco smoke. The 1964 report stated, "Calculations indicate that the nicotine absorbed (40 to 60 mg) from six cigars equals that from 30 cigarettes inhaled."[1] The Doll and Hill study of British doctors showed no significant differences among cigarette smokers between the CHD death rates of inhalers and noninhalers.[4] We know very little about the possible mechanisms which might explain why cigarette smokers have greater CHD death rates than nonsmokers while pipe and cigar smokers do not.

At the present stage of our knowledge, this anomaly is inexplicable. It is clearly a subject for further research. For now, we can only conclude that this discrepancy between the mortality rates of cigarette smokers vs those of cigar or pipe smokers is difficult to reconcile with the concept that tobacco smoking is causally related to excess deaths due to CHD.

Age of Smokers.—Virtually all the new studies confirm the finding of the 1964 report that death rates from coronary heart disease are relatively higher in male cigarette smokers compared to nonsmokers in middle age than in old age. In general, cigarette smokers more than 65 years of age have lower CHD mortality ratios and disabilities than those less than 65 years of age. This may, in part, reflect a selective survival effect in smokers and/or a diminishing risk for CHD among cigarette smokers relative to other influencing factors with advancing age.

It is possible that the relatively greater CHD mortality ratio among younger smokers is more a function of the differential age changes in CHD death rates of nonsmokers than of smokers. The point can be illustrated by comparing the CHD death rates according to age of smokers and nonsmokers with those of the general US population. In the US population in 1964, the death rate due to CHD of men ages 55 to 64 was 2.6 times greater than that of men ages 45 to 54, 2.2 times greater in ages 65 to 74 than in ages 55 to 64, and 1.9 times greater in ages 75 to 84 than in ages 65 to 74.[1] In comparison, Dorn's data[11] on veterans currently smoking cigarettes showed CHD death rate for men ages 55 to 64 to be 2.5 times greater than that of men ages 45 to 54, 1.9 times greater for ages 65 to 74 than ages 55 to 64, and 1.6 times greater in ages 75 to 84 than in ages 65 to 74. Further, in nonsmokers ("never smoked or occasionally only") from Dorn's study of veterans, CHD death rate for ages 55 to 64 was 10.0 times greater than that of ages 45 to 54, 2.0 times greater in ages 65 to 74 than in ages 55 to 64, and 2.2 times greater in ages 75 to 84 than in ages 65 to 74.

From these data, it would appear that the successive decade age increases in CHD death rates of

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the smokers parallel those of the US general population much more closely than do rates of the nonsmokers, with the nonsmokers particularly diverging from the general population in a far greater increase in CHD death rate from ages 45 to 54 to ages 55 to 64. Furthermore, in Dorn's study of veterans, the death rates for smokers are somewhat lower than those of the general public, and the death rates of persons who do not smoke are still lower. While it is difficult to make direct comparisons of death rates from one population to another, is it possible that the nonsmokers represent a very special and markedly singular group in the population, more so than the smokers?

Amount of Cigarette Smoking.—The Surgeon General's 1964 report states, ". . . the ratio of smokers' coronary death rates to those of nonsmokers increases progressively with the daily cigarette consumption." This increase in CHD death rates with increased amount of smoking was found in a number of studies.

However, an examination of the new data since the 1964 report reveals a very complex and hardly consistent picture. To begin with, a consistent positive gradient of CHD mortality with amount of cigarettes smoked is found only in the Dorn study,[11] Reid and co-workers' migrant study[14] (in British and Norwegian born but not in native born US men), and in white men of high social class in the Evans County, Georgia study.[15] "There is certainly no clear gradient [of CHD mortality] with number of cigarettes smoked" is the report by Doll and Hill in their survey of British doctors (a rising gradient is apparent in younger but not in older men), and no clear gradient is found in the Canadian veterans study,[13] and in the Negro and white men of low social class of the Evans County, Georgia study.[15]

Significantly, the majority of the new studies show inversions or inconsistencies in the gradient of mortality or morbidity with average number of cigarettes smoked daily. While it is true that in virtually all these instances, those who smoked the most cigarettes give consistently higher CHD and myocardial infarction rates than those who smoked the least, the consistency of the gradient is broken down as between the groups which smoked the least and the intermediate groups, with the intermediate rates the same or lower than the rates of the groups which smoked the least. Inversions between the groups which smoked the least (usually less than a pack a day) and the intermediate groups (at least one pack but less than two packs daily) are to be found in the combined Albany and Framingham study,[17] the Hammond study,[12] Reid and co-workers' migrant study (native born subjects),[14] the HIP investigation,[18] and the national health survey.[19]

Accordingly, it cannot be said that the new data confirm the results of the 1964 report with respect to a consistent rising gradient of CHD mortality with increased amounts of cigarettes smoked. On the contrary, the new data, with its many inconsistencies and inversions in the "rising gradient," indicate that this whole subject is not as clear cut as it appeared at first blush.

Parenthetically, it is to be noted that almost identical inversions in body build measurements according to amount of cigarettes smoked have been described by Seltzer in his study of morphological constitution and smoking habits of Harvard college graduates.[20]

Duration of Cigarette Smoking.—The 1964 report made no comment with regard to duration of smoking and CHD rates. Since the 1964 report, there have been three important studies which have dealt with this subject. The combined Albany and Framingham study[17] found an absence of association between duration of heavy cigarette smoking and risk of myocardial infarction. In Dorn's US veterans study there was also no significant relationship between duration of cigarette smoking and risk of death from CHD; Kahn summarized this by stating that there was ". . . an almost perfect fit of the data with a hypothesis of no relationship to duration."[11] And in the Canadian veterans survey there was no clear gradient of increasing CHD mortality with increasing years of smoking experience.[13] In fact, in this material, the mortality ratios for heart and circulatory diseases for those who had smoked cigarettes for 30 to 39 years (1.5) were lower than those of individuals who had smoked for a period of only 5 to 9 or 10 to 14 years (1.7 and 1.8, respectively).

It is notable that while duration of cigarette smoking is considered an important factor in connection with lung cancer mortality, the new evidence since the 1964 report points to an exoneration of this important element with respect to CHD. The evidence would appear to be consistent with the conclusion of the authors of the combined Albany and Framingham study that it is ". . . not any cumulative effect of inhaling cigarette smoke which precipitates myocardial infarction and death from CHD. . . ."[16]

This has led to the suggestion by the Framingham heart study that coronary heart disease is only *acutely* connected with cigarette smoking not *chronically* connected, acting by the "triggering of a lethal arrhythmia or thrombosis in subjects predisposed by an already compromised coronary circulation."[17] If this is indeed true, then the effect of smoking (by their suggestion) would be limited solely to those persons with "already compromised circulations." Does this signify that cigarette smoking is without deleterious effect on those with a normal, healthy coronary apparatus?

Inhalation.—The Surgeon General's 1964 report states, ". . . at each level of consumption the ratio (mortality ratio) increases with amount of inhalation reported by the smokers."

On this subject the new data give conflicting results. In the Doll and Hill study of British doctors,[13] the authors stated, "Only small and statis-

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tically insignificant differences were observed in coronary disease without hypertension (3% excess in inhalers). . . ." Furthermore, the death rate for noninhalers (5.09) was substantially higher than that for nonsmokers (3.29). We should not lose sight of this latter point. If more extended observations of British doctors beyond the present ten years' observations tend to confirm this finding, this would make it appear that something else apart from the inhalation of cigarette smoke is responsible for the higher death rate from CHD of smokers over nonsmokers. In this regard, other known risk factors and constitutional differences between smokers and nonsmokers would have to be given more serious consideration in the totality of the problem than has been accorded them up to now.

Hammond's prospective study,[13] on the other hand, exhibited a tendency for CHD death rates to increase with degree of inhalation. The data might have been more illuminating, however, if the noninhalers had not been lumped together with those who inhaled slightly. Again we find that Hammond's subjects who did not inhale or inhaled slightly had much higher death rates than the nonsmokers.

Ex-Smokers.—The 1964 report points out that, "men who stop smoking have a lower death rate from coronary disease than those who continue," and cites the six-year experience of the combined Albany and Framingham study[7] and Hammond and Horn's[11] 44 months follow-up of more than 187,000 American men.

The studies since have added considerably more material, but the nature of the results can hardly be said to clarify the subject. Thus, while Doll and Hill's study of British doctors,[8] Dorn's study of US veterans,[10] the Hammond study of American men,[12] and the study of Canadian veterans[11] give lower CHD rates for ex-smokers than of those currently smoking cigarettes, higher CHD rates are found among ex-smokers than among those currently smoking cigarettes and nonsmokers in the Tecumseh, Michigan study,[7] Reid and co-workers' study of migrants,[14] and the national health survey.[15] The combined Albany and Framingham study[16] shows former cigarette smokers with a lower CHD death risk than nonsmokers, and about the same level of CHD risk for fatal and nonfatal myocardial infarction as between former cigarette smokers and nonsmokers. The authors state, "The risk of CHD or death for ex-cigarette smokers in these two populations (Albany and Framingham) was nearly equal to the risk for those who never smoked . . ."

The mortality ratios of ex-cigarette smokers found in Dorn's data recede to an intermediate position between the corresponding figures for current smokers and nonsmokers, and that former cigar and pipe smokers have higher mortality ratios than those who continue smoking (as Dorn had reported earlier)." Dorn had suggested that many smokers may have stopped smoking because of ill health, but did not understand why this should be true for cigar and pipe smokers but not for cigarette smokers. For this reason, Kahn excluded from his calculations those individuals who had stopped smoking because of doctors' orders, but the effect persisted among cigar and pipe smokers just the same. Kahn does not find "obvious" why this effect persists. Some complications were also apparent in the Hammond study.[12] Ex-cigarette smokers who quit recently (less than one year ago for those who formerly smoked 1 to 19 cigarettes a day and less than five years ago for those persons who smoked 20 or more cigarettes a day) had CHD death rates as high as or higher than persons currently smoking cigarettes. This seemingly anomalous finding was further investigated in another study by Hammond and Garfinkel[17] in which ill health was suggested as a complicating factor in stopping smoking or reducing cigarette consumption. They reported that the bias introduced by the influence of ill health on smoking habits "makes it difficult to evaluate the degree of benefit derived from giving up smoking, and even more difficult to determine whether giving up the habit results in a reduction of death rates soon after."

Further conflicting results are to be found with respect to the first years after smoking is stopped and the long-term cessation of smoking. A sharp fall in CHD mortality is seen in the Doll and Hill study[8] in the first five years after the subjects stopped smoking (followed by a rise in the next period), but only moderate declines are to be found in the early years following discontinuance of smoking in Dorn's US veterans[10] and Hammond's American men.[12] The CHD rates of ex-smokers, after the longest period of cessation of cigarette smoking, fall to a level *below* that of persons currently smoking cigarettes but still *higher* than nonsmokers in the Doll and Hill,[8] Dorn,[10] and Canadian veterans studies,[11] and in the Hammond survey of the category of persons who smoked 20 or more cigarettes a day.[12] In the Hammond study, the CHD death rate dropped to the level of nonsmokers for the persons who smoked 1 to 19 cigarettes a day.

The extreme difficulties, in these kinds of studies, of clearly unraveling the effect of discontinuance of cigarette smoking on CHD rates is recognized by Doll and Hill,[8] Kahn,[11] Hammond and Garfinkel,[17] Epstein et al,[11] Reid et al,[14] K[illegible][11] and others. Doll and Hill, who gave much attention to this subject, pointed out, for example, that much of the fall of mortality with discontinuance of smoking ". . . may be an artifact, due merely to the selective failure of doctors to give up smoking when they are already ill."[8] Epstein et al, in explanation of their higher CHD rates of ex-smokers relative to both current smokers and nonsmokers, have said that their finding ". . . is to be expected, since persons with disease are more likely to discontinue the habit."[11] They all make the point that

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the bias introduced by ill health on smoking habits "dirties up" the data of ex-smokers and makes it therefore difficult to establish clear-cut trends and effects.

Summary

With this presentation of the additional information since the Surgeon General's 1964 report on the subject of smoking and coronary heart disease (considering the epidemiological studies only), we are now able to assess the nature of the evidence which has led to the extension and magnification of the claims of the effect cigarette smoking has on mortality and disability from CHD made by numerous people.

The conclusion of the Surgeon General's 1964 Report that male cigarette smokers have a higher death rate from CHD than men who do not smoke has been confirmed in the new studies published since the report was issued. This conclusion must be accepted as an established observation. But the question still remains as to the interpretation to be given to this statistical observation. The most such an epidemiological observation " . . . can do is to demonstrate the existence of a relationship between cigarette smoking and various health characteristics; it cannot establish any existing relationship as a causal one,"[5] and ". . . inferences on causality cannot depend on the demonstration of association alone."[6] The first phase of the epidemiological approach to a disease problem is the determination of the statistical association; the second phase is the derivation of biological inferences from the pattern of statistical association."

What inferences, then, may be drawn from the additional epidemiological evidence which has appeared since the 1964 report? And particularly, since the 1964 report concluded ". . . but it is not clear that the association has causal significance," what new inferences may be drawn with respect to causality?

Our survey of the new epidemiological evidence has indicated that, for all practical purposes, pipe or cigar smoking is not associated with excess deaths and disabilities due to coronary heart disease (CHD), leaving cigarette smoking as the focus of necessary attention. The weight of evidence, at the moment, is that angina pectoris as the sole or initial manifestation of CHD is probably unrelated to cigarette smoking. There are still some lingering questions with regard to the prevalence data in this regard, but conclusions drawn from prevalence data are generally considered less reliable than incidence rates. This would leave myocardial infarction (and sudden deaths) as the principal conditions statistically associated with cigarette smokers. In this connection, Doll and Hill have pointed out that a relationship with smoking is characteristic of only a little more than one-half the total number of deaths attributed to coronary thrombosis.[7] This erosion of postulated CHD smoking risks is further enhanced by the Framingham heart study which suggested that the effects of smoking is limited to those persons with "already compromised circulations."

With respect to amount of cigarette smoking, the new data do not confirm the finding of the Surgeon General's report of a consistent rising gradient of CHD mortality with increased amounts of cigarettes smoked, but on the contrary give a complex and hardly consistent picture showing a profusion of inconsistencies and inversions. The new data have in effect raised serious questions as to the validity of the 1964 report on this point. Duration of cigarette smoking has been found to be unassociated with excess CHD mortality in cigarette smokers in the new data, and conflicting results are obtained with regard to the effect of inhalation. Finally, the new data dealing with the effect of discontinuance of cigarette smoking (a subject considered of such great significance in lung cancer mortality) frequently give contradictory and inconsistent findings, and pose a virtually insoluble problem as to valid interpretations and conclusions that may be drawn from such data in the present study designs. The bias introduced by the influence of ill health on smoking habits makes it extremely difficult to determine whether giving up the habit actually results in a reduction of death rates soon after. Accordingly, in some respects the epidemiological evidence is less clear now than at the time of the 1964 report.

It is, therefore, difficult to see from the new epidemiological data how valid causal inferences can be drawn that *cigarette smoking* is linked to excess CHD deaths or that the excess CHD deaths are "*caused by*" cigarette smoking. We do not know whether or not there is a causal connection between cigarette smoking and increased deaths from coronary heart disease.

The present state of our knowledge still suggests (as the Surgeon General's Advisory Committee's Report on Smoking and Health stated in 1964) that "male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance."

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Epidemiological Studies

The results of epidemiological studies on the relationship of smoking to serum lipid levels have not been consistent. Several studies reported no significant difference in serum cholesterol (*56, 30, 61, 150*) and triglyceride levels (*30, 61*) between smokers and nonsmokers. In their study of twins, Blomstrand, et al. (*11*) state that prolonged smoking had an insignificant effect on all serum lipid levels in their monozygotic twins and only elevated phospholipids in their dizygotic group. However, they quote a personal communication from Carlson, et al. who found elevated trigyceride levels in smokers in a prospective study of 6,000 persons.

In a very comprehensive study of 637 former naval aviation cadets over a period of 25 years, Harlan, et al. (*56*) investigated the relationship of various constitutional and environmental factors to serum lipid and lipoprotein levels. They found that serum Sf 0–12 (beta) lipoproteins and cholesterol levels were related to cigarette smoking and that the duration of smoking also had a significant correlation. The authors felt that the relationship of smoking to these lipids was presumably direct, because cigarette smoking did not correlate with other factors related to lipids.

Experimental Studies—Animal

Studies in dogs of the immediate effects of tobacco smoke inhalation and nicotine administration showed an increase in serum triglycerides but not cholesterol, in addition to a rise in free fatty acids (*76*). There were no differences in cigarette, cigar or pipe smoke effects when the depth of inhalation was kept constant. Chronic administration of nicotine in dogs resulted in a 50 percent rise in serum cholesterol levels but did not affect triglycerides (*82*). Kershbaum, et al. (*83*) have also shown that pronethalol (a beta-receptor blocker) inhibits the serum-free fatty acid and triglyceride rise induced by nicotine in dogs.

In studies of the lipid and atherogenic effects of chronic nicotine administration in cholesterol-fed rabbits, one report found no effect in serum lipid levels but a significantly higher incidence of aortic fibrosis (*51*). Other investigators found that nicotine increased the amount of cholesterol in the blood and the intensity of lesions in the aorta (*23*). In cholesterol-fed rabbits administered vitamin D, Hass, et al. (*59*) found that nicotine induced severe calcific athero-arteriosclerosis and occlusive thromboarteritis, especially conspicuous in cardiac, smooth and skeletal muscle.

Astrup (*2*) has shown that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure had a marked atherogenic effect.

Gudbjarnason (*52*) has shown that chronic nicotine administration in dogs leads to a diminution in the rate of cholesterol turnover.

Studies in Humans

It has previously been reported (*73*) that cigarette smoking mobilizes free fatty acids, resulting in increased plasma concentrations. It was also found that this effect of smoking was the result of increased sympathetic and adrenal activity initiated by the absorbed nicotine (*84*), the latter having no direct lipolytic action in adipose tissue (*35*). This response to smoking has now been confirmed by other investigators (*11, 90, 110*).

Studies in man, on the immediate effect of cigarette smoking, have shown no effect on serum concentrations of lipoproteins and lipoprotein lipids (cholesterol, phospholipids, triglycerides) (*78, 92, 116*). In a recent study, however, an increase in serum beta-lipoproteins was observed 10 minutes after smoking (*72*).

In a study of the comparative effects of cigarette, cigar and pipe smoking on free fatty acid mobilization and catecholamine excretion, cigarette smoking was found to have a much greater effect (*81*). Less nicotine absorption in cigar and pipe smoking, due to the absence of inhaling, was considered to be the explanation for the milder biochemical effects with these two forms of smoking (*82*). Kershbaum, et al. also compared the effects of various types of cigarettes on these parameters (*79*). They found no difference in free fatty acid and catecholamine response or nicotine absorption with several brands of filter and non-filter cigarettes. Cigarettes containing shredded lettuce leaf had no effect.

In other lipid studies it was observed that smoking might increase the tendency of human blood serum to crystallize cholesterol (*87*).

Kershbaum has also shown that cigarette smoking increases the blood steroid levels in humans (*86*).

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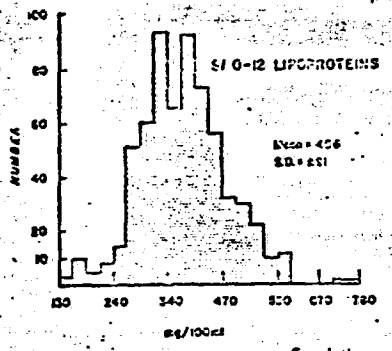
Epidemiological Studies Relating to Serum Lipids. Like other types of studies in this page, the epidemiological studies comparing nonsmokers and smokers indicate conflicting results. The negative studies are not discussed. The Results of (150) Van Buchem et al. are reproduced below.

The positive results of (56) Harlan et al. are described in the document. The differences in population and nature of diet may account for conflicting results. Note that Harlan et al. also identified skin folds, uric acid and weight gain to correlate with lipoprotein fraction.



Variable	Cumulative Multiple r
SMOKING - AMOUNT	0.144
SKINFOLDS - CHEST	.188
URIC ACID	.221
WEIGHT GAIN 24 - 45 yr. (-)	.241
Fasting glucose	.252
Family history - father	.265
Mesomorphy	.267
Family history - mother	.274
PBI (-)	.278

FIGURE 1. Frequency distribution of values for Sf 0-12 (beta) lipoproteins and factors correlated with levels of these lipoproteins. Factors having correlations significant at 5% level or greater are spelled out in capital letters. Skinfolds are a measurement of subcutaneous adipose tissue at the site noted. PBI = protein-bound iodine. See text for description of analytical methods.

The Sf 0-12 lipoproteins (beta-lipoprotein), which are composed predominantly of cholesterol (51%) and phospholipid (28%) but little triglyceride (6%), are related to cigarette smoking, skinfold thickness of the chest, uric acid, and have a negative relation up to weight gained from age 21 to age 45. Although the number of cigarettes smoked was selected by this analysis, the duration of cigarette smoking also had a significant correlation, these variables being highly interrelated. Similarly, skinfold thickness of the chest and back are closely related, and selection of the chest measurement excluded that of the back. However, skinfold thickness in other areas was not related to these lipoproteins. The minor contribution of protein-bound iodine (PBI) to the multiple correlation is of interest because of the close relationship between pathological

TABLE XIV. Serum-cholesterol level in smokers and non-smokers

	Serum cholesterol (mg %)		
	0—209	210—249	>250
Non-smokers	32	44	41
Light smokers	18	14	10
Moderate smokers	70	76	60
Heavy cigarette smokers	96	123	127
Heavy cigar smokers	23	24	29
Heavy smokers	6	12	11
Heavy pipe smokers	11	20	11
Unknown	1	1	
Total	257	314	289

Several times the nature of the diet of all men was examined with different methods. No correlation was found between the nutrition and the serum cholesterol level. The diet of the men before they suffered from atherosclerotic complications was not different from the diet of the whole group. No correlation was found between smoking or non-smoking, and the degree of smoking, and the serum cholesterol content.

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The 1967 Report reviewed the effects of smoking on *in vitro* thrombus formation, varying platelet characteristics and other serum factors associated with blood coagulation. It is not in the scope of this report to go into a detailed analysis of blood coagulation and/or thrombosis. However, the role of smoking and blood lipids on thrombogenesis will be briefly discussed, as they relate to thrombosis and cardiovascular disease.

Catecholamines

The role of catecholamines (especially epinephrine) in thrombogenesis must be stressed (*111*). The nicotine-induced catecholamine release, which plays a major role in cardiovascular dynamics might also be the mediating factor in the relation between cigarette smoking and thrombosis. Ardlie (*1*) has shown that catecholamines enhance ATP or ADP induced platelet aggregation. ADP and noradrenaline in low concentration (up to 0.05 μg./ml.) were found to increase platelet mobility (*55*). The reverse was true in higher concentration. Rowsell (*123*) has shown increases in both thrombus formation in an extracorporeal system and clotting time in silicon-coated tubes with moderate doses of epinephrine. Large doses gave values closer to the control state. Besterman (*8*) has shown a diurnal variation in "platelet" stickiness which might be associated with diurnal variations in catecholamine release. Glynn (*48*) found no difference in platelet aggregation between smokers and nonsmokers.

Shimamoto (*133*) proposes that epinephrine has a primary effect on the arterial wall causing the release of a thromboplastin-like substance which then leads to increased platelet aggregation. An autopsy study in humans by Auerbach (*3*) showed increased fibrous thickening in the walls of arterioles and small arteries of 5 organs, in smokers as compared to nonsmokers. This effect might be secondary to platelet changes which then caused damage to the arterial wall. As discussed earlier in the study by Hass (*59*), in which rabbits on a high cholesterol and vitamin D diet were given nicotine, at the site of the occurrence of thrombus there was usually an inflammation of the arterial wall.

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Blood Lipids

Conner, et al. (*26*) and Warner, et al. (*152*) have described various experiments in dogs and rabbits, in which infusion of long-chain saturated free fatty acids caused extensive thrombosis and death. *In vitro* coagulation and platelet aggregation were also increased. Long-chain unsaturated free fatty acids, however, did not have these effects although microscopic platelet aggregation was observed (*66*). *In vitro* studies have shown that linoleic and linolenic acids might have a protective effect against platelet aggregation induced by long-chain saturated fatty acids (*73, 101*).

The rise in plasma-free fatty acids which follows cigarette smoking was associated with increased platelet adhesiveness (*110*). The long-chain fatty acid-induced platelet aggregation was suggested to be due to ADP release from platelets (*58*). Harrison (*57*) suggests that *in vitro* platelet adhesiveness tests are influenced by ADP release from damaged red cells and that the platelet change might really be a reflection of red cell abnormalities.

Bray (*14*) found that coronary heart disease patients have an exaggerated platelet adhesiveness in response to ADP or ATP.

Several studies have shown disturbances in lipid and carbohydrate metabolism in coronary heart disease patients (*24, 55, 156*).

Kurien (*95*) postulates that the increases in free fatty acid levels immediately after either an acute myocardial infarction or cerebrovascular accident result from tissue anoxia with a secondary catecholamine release, which then leads to the increases in free fatty acids. Malhrotra (*103*) studied two population groups in India. There was no difference in the cholesterol, trigiyceride, and free or esterified fatty acid levels between the two groups. However, the incidence of coronary heart disease was much higher in the population whose diet and fat absorption predispose to an abundance of long-chain fatty acids.

A majority of coronary heart disease patients have an abnormal glucose tolerance test. In most of these patients there is a greater decrease in free fatty acids in response to glucose and a slower return to normal values (*24, 156*).

Soloff and Schwartz (*156*) have determined two subgroups of these patients: one "A", in which the free fatty acid response to glucose resembled a normal curve except for an exaggerated rise after 5 hours; another "B", in which the free fatty acid response to glucose resembled that of diabetics, there being a slower decrease and a subnormal return of free fatty acid levels after 5 hours. The significant effect, however, is that type "B" patients had a relative hyporesponse of stearic acid (long-chain saturated) decline with a relatively decreased rise in linoleic acid (long-chain unsaturated) after 5 hours.

These findings may be related to the effect of saturated and unsaturated fatty acids on blood coagulation and suggest further research to delineate the specific fatty acids elicited after smoking and in coronary heart disease patients.

Cardiovascular Response to Smoking and/or Nicotine

This section should be read in conjunction with the findings reviewed in the 1967 report.

Experimental Studies

Nadeau, et al. (*112*) cannulated the sinus node artery in anesthetized dogs and noted chronotropic changes in response to doses of nicotine ranging from 1.0 to 100 μg./ml. Intranodal atropine abolished bradycardia and intranodal propranolol or hexamethonium abolished tachycardia. Nicotine inhibited the effects of cervical vagus nerve stimulation without modifying the response to intranodally injected acetylcholine. Nicotine did not inhibit the effect of stellate ganglion stimulation. These results illustrate the varying effects of nicotine under experimental conditions on the complicated neural and humoral mechanisms affecting heart rate and rhythm.

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(112) Nadeau, R. A., James, T. N. Effects of nicotine on heart rate studies by direct perfusion of sinus node. American Journal of Physiology 212(4): 811-816, April 1967.

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Blood Lipids and Platelet Aggregation. Most of the articles cited in this section do not relate to cigarette smoking or to nicotine. Out of the 17 articles, there is only one which describes the acute effects of smoking on blood lipids. There were 12 patients who took smoking tests and sham-smoking test. The document quotes only one part of the Conclusions. The other statements omitted relate to the "variable effect of smoking on platelet adhesiveness". It should also be noted that sham-smoking caused the same effects as smoking. The Discussion and Summary are as follows:

(170) Murchison and Fyfe 1966

Discussion

The significant rise in plasma-N.E.F.A. after smoking, with no significant alteration in cholesterol and triglyceride, confirms the findings of previous workers (Kershbaum et al. 1961). It is interesting that sham-smoking was followed by a similar rise in plasma-N.E.F.A. in 5 of the 12 tests. The fact that the rise followed a steady basal period suggests that the effect was due to sham smoking rather than repeated venepuncture, and might possibly be due to the embarrassment of puffing an unlit cigarette. The fact that sham smoking may produce physiological changes was recognised by Irving and Yamamoto (1963) in their investigation of the effects of cigarette smoking on cardiac output.

An increase in unsaturated fatty acids at the expense of saturated fatty acids has been found by other investigators when the total plasma N.E.F.A. is raised by stimuli other than smoking (Rothlin et al. 1962, Wood et al. 1965). It is somewhat surprising that the change after sham smoking was more striking than that after smoking, and that the change in pattern does not correlate well with the change in total plasma-N.E.F.A. level.

Some earlier workers reported that cigarette smoking elevated the blood-glucose (Lundberg and Thyselius-Lundberg 1931) but Rehder and Roth (1959) have suggested that the rise shown was due to stress rather than an effect of smoking. In our series the rise can be attributed to smoking per se.

The increased platelet count after smoking also seems to be a nicotine effect. This effect has previously been reported in an uncontrolled study by Grassi and Caltabiano (1956). The mechanism is obscure, but may be a result of adrenaline release (Vaughan-Jones et al. 1963).

Platelet adhesiveness is known to be increased after myocardial infarction (Macdonald and Edgill 1957) and in disseminated sclerosis (Caspary et al. 1965, Payling Wright et al. 1965) and, since fatty-acid abnormalities have also been demonstrated in these conditions (James et al. 1957, Thompson 1966), a relationship between platelet adhesiveness and serum-fatty-acids has been suggested. The proposal has been supported by the in-vitro work of Kerr et al. (1965), who showed that saturated fatty acids induced greater platelet aggregation than unsaturated fatty acids, some of which seemed to have an inhibitory effect. Our results show that when the blood-glucose remained constant there was a good correlation between the changes in platelet adhesiveness and the changes in N.E.F.A. When the blood-glucose also altered (in the smoking-test) the relationship between the changes in platelet adhesiveness and N.E.F.A. was less close. In this situation, the rise in blood-glucose seemed to have a suppressive effect on platelet adhesiveness, since there was a negative correlation between the changes in blood-glucose and platelet adhesiveness.

Bridges et al. (1965) showed that platelet adhesiveness increased after an oral glucose load, but he was unable to show a correlation between the rise in blood-glucose and the rise in platelet adhesiveness. This situation, however, is quite different to the present one in which endogenous glucose is being mobilised. Bridges et al. (1965) also showed that the addition of glucose in vitro resulted in an increase in platelet adhesiveness, but this is contrary to the work of Hellem (1960) who was unable to demonstrate any effect within the physiological range for glucose.

We have not confirmed the findings of Ashby et al. (1965) of a significant increase in platelet adhesiveness after smoking. Although 7 cases showed a considerable rise in platelet adhesiveness following smoking, in 5 others in whom there was a marked rise in glucose the platelet adhesiveness fell. This effect was more evident in 2 patients who felt nauseated at the end of the smoking-period and who showed the largest increase in blood-glucose in association with delay in N.E.F.A. rise. Since Ashby et. al (1965) only measured platelet adhesiveness it is not possible to explain the discrepancy between his results and ours. It may be, however, that in the non-fasting state the blood-glucose response to smoking is less striking. The somewhat surprising finding of a significant increase in platelet adhesiveness after sham smoking is clearly associated with the unopposed effect of the rise in N.E.F.A. on which we have already commented.

Summary

Platelet adhesiveness, blood-glucose and plasma-lipids were estimated in 12 patients before and after smoking and sham smoking. Cigarette smoking elevated plasma nonesterified-fatty-acid levels and resulted in an increase in the proportion of unsaturated fatty acids at the expense of the saturated fatty acids. Smoking was also followed by a significant rise in blood-glucose and a transient increase in the total platelet count. The variable effect of smoking on platelet adhesiveness seemed to be due to opposing actions of changes in nonesterified fatty acid and glucose levels. A rise in plasma nonesterified fatty acid was associated with increased platelet adhesiveness, whereas a rise in glucose inhibited platelet adhesiveness.

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